**UNITED STATES ENVIRONMENTAL PROTECTION AGENCY**
**WASHINGTON, D.C. 20460**

**OFFICE OF**
**CHEMICAL SAFETY AND**
**POLLUTION PREVENTION**

# MEMORANDUM

**Date:** March 29, 2016

**SUBJECT:** Dicamba and Dicamba BAPMA Salt: Human-Health Risk Assessment for Proposed Section 3 New Uses on Dicamba-tolerant Cotton and Soybean

**PC Code:** 029801, 128931, 029802, 029806, 128944, 029803, 100094 & 129043
**Decision No.:** 432752, 467997, 463710
**Petition No.:** 2F8067 & 0F7725
**Risk Assessment Type:** Single Chemical, Aggregate
**TXR No.:** NA
**MRID No.:** NA

**DP Barcode:** D378366, D404917, D402514, D421306, D402551
**Registration No.:** 524-582-M1691, 524-ANO & 7969-GUL
**Regulatory Action:** Section 3 & R170
**Case No.:** 0065
**CAS No.:** 1918-00-9
**40 CFR:** §180.227

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And

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**TO:** Grant Rowland
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## 1.0 Executive Summary

Monsanto has submitted petitions PP# 0F7725 and PP#2F8067 requesting Section 3 registration for the use of dicamba on dicamba-tolerant soybean and cotton. For these petitions, Monsanto is requesting to establish new tolerances for dicamba-tolerant soybean forage at 45 ppm and for dicamba tolerant soybean hay at 70 ppm as a joint work-share project with Canada and Japan. Monsanto is also requesting to amend the cotton un-delinted seed tolerance from 0.2 ppm to 3.0 ppm and establish a new tolerance for cotton gin byproducts at 70.0 ppm. The proposed application is for pre- and post-emergence uses of dicamba on these dicamba-tolerant crops.

BASF has also submitted R170 new food-use registration requests for the dicamba BAPMA (N, N-Bis-(3-aminopropyl) methylamine) product on conventional crops as well as on dicamba-tolerant cotton and soybean. In support of this request, bridging data were provided to demonstrate equivalency of residues resulting from the BAPMA salt product with respect to the registered diglycolamine (DGA) salt. Included in the BASF petition are bridging data for another new formulation of dicamba which contains the diethylenetriamine (DETA) salt; registration of the DETA formulation of dicamba is not being requested at this time.

Dicamba (benzoic acid, 3,6-dichloro-2-methoxy-, aka 3,6-dichloro-*o*-anisic acid) is a selective systemic herbicide belonging to the benzoic acid chemical family and is currently registered for use on both soybeans and cotton as pre-plant applications and not as post emergence applications because crop injury could occur if it were to come in contact with roots, stems, or foliage. Dicamba is available for use in either acid or salt forms with registered uses being maintained on a wide variety of crop and livestock feed items. Dicamba also has registered uses for treatment on turf. Permanent tolerances are established under 40 CFR §180.227(a)(1) for dicamba and its 3,6-dichloro-5-hydroxybenzoic acid (5-hydroxydicamba) metabolite. Additional tolerances are established under 40 CFR §180.227(a)(2) for dicamba and its 3,6-dichloro-2-hydroxybenzoic acid (aka 3,6-diclorosalicyclic acid or DCSA) metabolite, as well as under 40 CFR §180.227(a)(3) for dicamba, 5-hydroxydicamba, and the DCSA metabolite.

The residue chemistry database for dicamba is complete. The nature of residues for dicamba-tolerant soybean and cotton is understood. No new revised tolerances on livestock commodities are required to support this petition. A number of enforcement methods exist for the determination of dicamba and its metabolites in soybean and cotton as well as in animal matrices.

Using the OECD calculation procedures, tolerances of 60 ppm for soybean forage and 100 ppm for soybean hay are recommended. The current tolerances of 10 ppm in soybean seed and 30 ppm in soybean hull are adequate. For cotton, the recommended tolerances of 3.0 ppm for cotton undelinted seed and 70 ppm for cotton gin byproducts are appropriate.

BASF has submitted new toxicology studies for the dicamba BAPMA salt (rat developmental, rat 28-day inhalation and rat 90-day oral studies) and a 28-day inhalation study on the dicamba acid, as well as an OECD 422 developmental/reproduction study for the BAPMA base.

Neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in studies in rats and rabbits at doses over 150 mg/kg/day. The rat reproduction study and the developmental studies in rats and rabbits showed no evidence (qualitative or quantitative) for increased susceptibility following *in utero* or postnatal exposure of dicamba acid or its salts. In the rabbit developmental toxicity study, an increased incidence of abortion (1/20 does) was seen at doses that also caused maternal toxicity, as evidenced by clinical signs of neurotoxicity. In a two-generation dicamba acid reproductive toxicity study, offspring toxicity was manifested as decreases in pup weight at a dose where parental toxicity was also observed. Dicamba is classified as "not likely to be carcinogenic to humans". Mutagenicity studies did not demonstrate mutagenic concern for dicamba. There was no evidence of dermal or systemic toxicity following repeated dermal application of dicamba acid or the salts at the limit dose (1000 mg/kg/day). There is no concern for immunotoxicity following exposure to dicamba. Following oral administration, dicamba is rapidly absorbed and rapidly excreted in urine and feces without significant metabolism. Dicamba has a low acute toxicity via the oral, dermal or inhalation route (Acute Toxicity Categories III or IV). It is an eye and dermal irritant but it is not a skin sensitizer.

An acute dietary risk assessment was conducted for the general population including infants and children based on clinical signs of neurotoxicity (ataxia, unsteady gait and convulsions) observed in maternal animals in a developmental toxicity study in rats with the dicamba BAPMA salt. An acute Reference Dose (RfD) of 0.29 mg/kg/day was established based on a Point of Departure (POD) of 29 mg/kg/day and the application of the conventional 100 inter- and intra-species uncertainty factors (UFs). An acute dietary risk assessment was not conducted for females 13-49 since toxicity endpoints of concern attributable to a single dose (exposure) were not identified in the database. A chronic dietary risk assessment was conducted based on decreased body weights in the offspring in a two-generation reproduction toxicity study with the DCSA metabolite. A chronic RfD of 0.04 mg/kg/day was established based on a POD of 4 mg/kg/day and the application of the conventional 100 UFs. The POD selected would address the suite of toxic effects seen with the acid, salts and the metabolites of dicamba. Risk assessment for incidental oral exposure for children is based on a decreased pup weight in the reproduction study with dicamba acid. The Level of Concern (LOC) for this scenario is a target Margin of Exposure (MOE) of 100, which includes the conventional 100 UF. A quantitative dermal assessment is not required for dicamba acid or the BAPMA salt since no systemic toxicity was seen at the limit dose in rats and/or rabbits with dicamba or its salts and there was no concern for susceptibility based on the findings of the developmental and reproduction studies. Potential risks from occupational and residential exposure via the inhalation route will be assessed using PODs and endpoints of concerns derived from route-specific inhalation toxicity studies conducted with the dicamba acid and dicamba BAPMA salt.

The acute and chronic dietary (food and drinking water) exposure estimates are not of concern for the U.S. population or any population sub-group. For the acute dietary assessment, the most highly-exposed population sub-group is all infants (<1 year old) at 31% of the aPAD. For the chronic dietary assessment, the most highly-exposed population sub-group is children 1-2 years old at 42% of the cPAD.

There are no proposed residential uses at this time for either dicamba or the dicamba BAPMA salt; however, there are existing residential turf uses of dicamba that have been reassessed in this document to reflect updates to HED's 2012 Residential Standard Operating Procedures (SOPs). There is no potential hazard *via* the dermal route for dicamba; therefore, the handler assessment includes only the inhalation route of exposure, and the post-application assessment includes only the incidental oral routes of exposure. The residential handler (adult) and post-application (children 1 to <2 years old) risk estimates are not of concern for dicamba for all scenarios (i.e., all inhalation MOEs ≥ 30 and incidental oral MOEs ≥ 100).

A quantitative assessment of non-occupational exposure and risk resulting from spray drift was conducted for the BAPMA salt, which results in no risk estimates of concern (i.e., all MOEs ≥ 100) at the field edge for aerial and ground boom applications at the maximum agricultural application rate of 1 lb ae/A. Since the dicamba residential turf application rate is equal to or higher than the proposed uses of dicamba on agricultural crops, the residential turf scenario is protective of any exposure via spray drift from the proposed agricultural dicamba applications.

The potential non-occupational exposure to vapor phase dicamba and BAPMA residues emitted from treated fields from the proposed uses has been evaluated in this assessment. Volatilization modeling was completed using PERFUM as well as chemical- and formulation-specific flux data. The results indicate that volatilization of dicamba and BAPMA from treated crops does occur and could result in bystander exposure; however, results of PERFUM modeling indicate that airborne concentrations, even at the edge of the treated fields, are not of concern.

The acute and chronic aggregate exposure estimates are equal to the acute and chronic dietary assessments and are not of concern for the U.S. population or any population sub-group. The short-term aggregate (food, water, and residential) assessment for children is not of concern since the MOE is 3600 (LOC = 100). For adults, there is no short-term aggregate assessment since there is no dermal hazard identified and the inhalation effects are not systemic. Dicamba is not likely to be carcinogenic to humans, thus a quantitative cancer risk is not applicable and not assessed.

Occupational handler and post-application exposures are anticipated from the proposed uses. For the proposed uses of dicamba, the label-required personal protective equipment (PPE) for mixers, loaders, applicators and other handlers includes a long-sleeved shirt and long pants, socks, shoes, and chemical-resistant gloves (except for applicators using ground boom equipment, pilots or flaggers). For the proposed uses of dicamba BAPMA salt, the label-required PPE for mixer, loaders, applicators and other handlers includes long-sleeved shirt and long pants, shoes plus socks. The restricted entry interval (REI) on the proposed labels is 24 hours. The occupational handler inhalation risk estimates are not of concern for dicamba (i.e., MOEs ≥ 30). Most occupational handler inhalation risk estimates are of concern for dicamba BAPMA salt (inhalation MOEs < LOC of 300) based on the label-required PPE (i.e., no respiratory protection). Some handler risk estimates are still of concern with the maximum respiratory protection/engineering controls. Since there is no potential hazard via the dermal route for dicamba, a quantitative occupational post-application dermal risk assessment was not completed. The REI on the proposed labels (24 hours) is based on WPS requirements.

## 2.0 HED Recommendations

HED has no objection to the registration and establishment of tolerances for dicamba uses requested by Monsanto on dicamba-tolerant cotton and soybean provided the label modifications are made as outlined in Section 2.3 below. There are also no residue chemistry considerations that would preclude registration of the new BAPMA salt formulation of dicamba requested by BASF. HED has no objection for establishing the use of the BAPMA end-use product on conventional crops as well as on dicamba-tolerant cotton and soybean. The specific tolerance recommendations are provided in Section 2.2.2.

## 2.1 Data Deficiencies

Provided a revised Section F reflecting the recommended tolerance levels listed in Table 2.2.2, is provided, there are no residue chemistry, toxicology or exposure data deficiencies that preclude establishing permanent tolerances on soybean and cotton raw agricultural commodities (RACs) for dicamba.

## 2.2 Tolerance Considerations

### 2.2.1 Enforcement Analytical Method

Adequate methods are available for the enforcement of the newly proposed cotton seed and cotton gin byproducts as well as soybean seed, forage and hay tolerances. The existing analytical method AM-0691B-0297-4 is the latest revision of the Agency validated method AM-0691B-0297-2 which was submitted to FDA for inclusion into PAM volume II.

An independent laboratory validation of the liquid chromatography/mass spectrometer/mass spectrometer (LC/MS/MS) method, BASF Method D0902, used for analyzing the field trial samples in the bridging studies has also been provided for assessment. BASF Analytical Method D0902 meets these conditions depicting the suitability of an enforcement methodology. Pending editorial revisions recommended by the independent validation laboratory, HED determines the BASF method to be adequate for the tolerance enforcement of crops.

Dicamba is completely recovered through the FDA multi-residue method (MRM) testing protocols using Section 402 E2 of Protocol B, but is partially recovered using Section 402 E1 of Protocol B (Appendix II of PAM Volume I). BASF Corporation has recently submitted multi-residue testing data for the dicamba metabolites of concern 5-OH dicamba and DCSA (MRID 48001304) and is currently under review by the Agency.

Analytical standards for dicamba and its metabolites of concern are currently available in the EPA National Pesticide Standards Repository (personal communication with Theresa Cole, BEAD, 08/31/2015). The current stock of standards is set to expire on 02/01/2017.

### 2.2.2 Recommended Tolerances

The current tolerance expression is compliant with HED's Interim Guidance on Tolerance Expressions (05/27/2009, S. Knizner). The newly proposed tolerances should be established under 40 CFR §180.227(a)(3) as noted below in Table 2.2.2. The 40 CFR §180.227(a)(1) citation for dicamba currently lists a 0.2 ppm tolerance for cotton, undelinted seed. This entry in the CFR should be removed, and replaced with the tolerances shown above under 40 CFR §180.227(a)(3).

**Table 2.2.2. Tolerance Summary for Dicamba.**

| Commodity | Proposed Tolerance (ppm) | HED-Recommended Tolerance (ppm) | Comments (*correct commodity definition*) |
|---|---|---|---|
| Cotton, gin byproducts | 70.0 | 70 | |
| Cotton, undelinted seed | 3.0 | 3.0 | |
| Soybean, forage | 45.0 | 60 | |
| Soybean, hay | 70.0 | 100 | |

### 2.2.3 Revisions to Petitioned-For Tolerances

Tolerances for soybean forage and hay proposed by the petitioner were estimated using the NAFTA MRL calculator. EPA's recommended tolerances, which differ from the proposed tolerances, were derived using the OECD MRL calculation procedures, which is the Agency's current standard for determination of tolerances.

### 2.2.4 International Harmonization

The review of dicamba-tolerant soybean studies is a global joint review led by the U.S. with Canada and Japan as participating reviewers. US EPA and PMRA (Canada) previously established a harmonized tolerance (MRL) for soybean on seed at 10 ppm. There are currently no Mexican, Canadian or Codex MRLs established for soybean forage and hay or for cotton gin byproducts. There are MRLs of 0.2 ppm in Mexico and 0.04 ppm established by Codex on cotton seed. Mexico adopts existing U.S. crop tolerances for export purposes, which in this instance, is the current cotton undelinted seed tolerance of 0.2 ppm. Because the registrant is now requesting a late season use of dicamba on dicamba-tolerant cotton, the currently established international tolerances are not adequate to cover residues likely from the newly proposed use in the U.S. In addition, the dicamba residues of concern for dicamba-tolerant cotton also include the DCSA metabolite which is not found nor regulated in the other common varieties of cotton. Therefore, harmonization with respect to the tolerance expression is not possible at this time for cotton seed. Since there are no international tolerances on cotton gin byproducts, there is no issue of international harmonization relevant to that tolerance (Appendix D).

## 2.3 Label Recommendations

### 2.3.1 Recommendations from Residue Reviews

An amended Section B for the Monsanto cotton petition (PP#2F8067) is required noting that no more than two (2) post-emergence applications may be made past the first open boll stage when

treating dicamba-tolerant cotton. This also requires BASF to provide an amended Section B noting this same restriction for the post-emergence treatment of dicamba-tolerant cotton on the dicamba BAPMA product label as well.

### 2.3.2 Recommendations from Occupational Assessment

Most occupational handler inhalation risk estimates are of concern for dicamba BAPMA salt based on the label-required PPE (i.e., no respiratory protection). Some handler risk estimates are still of concern with the maximum respiratory protection (i.e., PF10 respirator)/ engineering controls (see Table 9.1.3).

### 2.3.3 Recommendations from Residential Assessment

None.

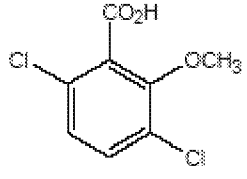
## 3.0 Introduction

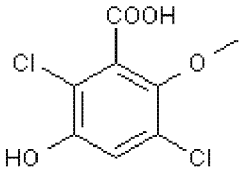
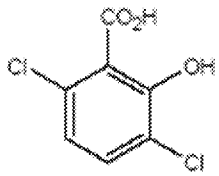
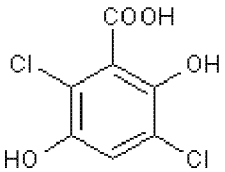
Dicamba, 3,6-dichloro-2-methoxybenzoic acid, is a selective benzoic acid herbicide registered for controlling a wide variety of broadleaf weeds and woody plants prior to their emergence. It has similar signaling properties to natural auxins which induce abnormal and uncontrollable growth to disrupt normal plant functions at high concentrations. Dicamba end-use products are available as either acid or salt formulations with registered uses being maintained on a wide variety of crop, livestock feed commodities and turf.

Monsanto has developed dicamba-tolerant varieties of soybean and cotton seeds capable of receiving dicamba treatments up to seven days before harvest. A dicamba mono-oxygenase (DMO) gene is introduced into dicamba-tolerant seeds to encode the enzyme dicamba *O*-demethylase to convert dicamba into the non-herbicide metabolite 3,6-dichlorosalicylic acid (DCSA), thus causing the plant to tolerate the herbicidal effect of dicamba. Table 3.1 shows the chemical names and structures of dicamba and its residues of concern.

## 3.1 Chemical Identity

**Table 3.1. Test Compound Nomenclature: Dicamba and its Residues of Concern.**

| Compound | Chemical Structure |
|---|---|
| |  |
| Common name | Dicamba |
| IUPAC name | 3,6-Dichloro-*o*-anisic acid |
| CAS name | Benzoic acid, 3,6-dichloro-2-methoxy- |
| CAS # | 1918-00-9 |
| End-use product/EP | M1691 Herbicide (EPA Reg. No. 524-582) and Engenia Herbicide (EPA Reg. No. 7969-GUL) |

| | |
|---|---|
| Compound |  |
| Common name | 5-Hydroxy-dicamba |
| IUPAC name | 2,5-dichloro-3-hydroxy-6-methoxybenzoic acid |
| CAS name | Benzoic acid, 2,5-dichloro-3-hydroxy-6-methoxy- |
| CAS registry number | 7600-50-2 |
| Compound |  |
| Common name | DCSA; 3,6-dichlorosalicylic acid |
| IUPAC name | 3,6-dichloro-2-hydroxybenzoic acid |
| CAS name | Benzoic acid, 3,6-dichloro-2-hydroxy- |
| CAS registry number | 3401-80-7 |
| Compound |  |
| Common name | DCGA; 3,6-dichlorogentisic acid |
| IUPAC name | 2,5-dichloro-3,6-dihydroxybenzoic acid |
| CAS name | Benzoic acid, 2,5-dichloro-3,6-dihydroxy- |
| CAS registry number | 18688-01-2 |

## 3.2 Physical/Chemical Characteristics

Technical dicamba is a light cream/tan colored solid composed of granules, lumps, flakes. Dicamba has a vapor pressure of $3.4 \times 10^{-5}$ mm Hg at 25°C and is known to volatize in the field. Dicamba is not expected to bioaccumulate in aquatic organisms because it is an anion at environmental pH values ($pK_a$=1.9). Dicamba is not significantly broken down by water or light. Aerobic soil metabolism is the main degradative process for dicamba. A single observed half-life for dicamba was six (6) days with the formation of the intermediate degradate 3,6-dichloro-2-hydroxybenzoic acid (aka 3,6-diclorosalicyclic acid or DCSA). DCSA was found to degrade roughly at the same rate as dicamba. Dicamba was found to be very soluble (6100 ppm) and very mobile ($K_{OC}$=13.4) in the laboratory. Results from two acceptable field dissipation studies conducted with the dimethylamine salt of dicamba indicated it dissipated with a half-life of 4.4 to 19.8 days. DCSA was the major degradate in both studies with both DCSA and dicamba being found in soil segments deeper than 10 cm. If any dicamba did reach anaerobic groundwater, it would be somewhat persistent due to its observed anaerobic half-life of 141 days. Given these factors dicamba and the DCSA metabolite may remain evident in water to reach water supplies for human consumption. See Appendix B for a table of physio-chemical properties of dicamba.

## 3.3 Pesticide Use Pattern

The dicamba product used for treating dicamba-tolerant soybean and cotton proposed by Monsanto for registration is the M1691 Herbicide (EPA Reg. No. 524-582) which is a soluble (flowable) concentrate formulation. This end–use product contains 56.8% active ingredient in the form of the DGA salt of dicamba (equivalent to 4.0 lb acid equivalents (ae)/gal). A summary of the proposed directions for use taken directly from the supplemental M1691 herbicide label provided by the registrant are presented below in Table 3.3.1.

The submitted data are adequate and reflect the maximum use rates listed in M1691 Herbicide Supplemental labeling.

**Table 3.3.1. Summary of Directions for Use of Dicamba.**

| Formulation [EPA Reg. No.] | Applic. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|---|
| *MON 88701 Cotton* | | | | | | | | |
| M1691 4.0 lb ae/gal SL [524-582] | Pre-plant, at planting, and Pre-emergence Broadcast (20 gal/A) | 1.0 | NS[5] | 1.0 | 2.0 | 7 | 7 | Use of a COC or MSO is not recommended with Roundup branded herbicides. These adjuvants are only used when other products require them. For best results apply at min spray rate of 10 GPA. Apply with ground equipment only; aerial application is prohibited. |
| | Post-emergence, Broadcast (20 gal/A) | 0.5 | NS | 2.0 | | | | |
| *Soybean* | | | | | | | | |
| M1691 4.0 lb ae/gal SL [524-582] | Pre-plant, at planting, and Pre-emergence Broadcast (20 gal/A) | 1.0 | NS | 1.0 | 2.0 | 7 | 7 | The maximum rate for any single, in-crop (post-emergence) application must not exceed 0.5 lb |

| Table 3.3.1. Summary of Directions for Use of Dicamba. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Formulation [EPA Reg. No.] | Applic. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
| | Post-emergence, Broadcast (20 gal/A) | 0.5 | NS | 1.0 | | | | dicamba a.e. per acre. A second post-emergence application may follow up to the R1 reproductive stage. Apply with ground equipment only; aerial application is prohibited. |

[1] ae = Acid Equivalents
[2] RTI = Re-Treatment Interval
[3] PHI = Pre-Harvest Interval
[4] COC = Crop Oil Concentrate; MSO = Methylated Seed Oil.
[5] NS = Not Specified

For treating dicamba-tolerant cotton, the M1691 Herbicide (EPA Reg. No. 524-582) product label allows growers flexibility in the application of dicamba to control weeds. The residue data provided examining this broad pattern of use shows that later post-emergence treatments give much higher residues then those made at earlier growth stages. Following the pattern of late season use demonstrated by the field trial data, no more than two (2) post-emergence applications may be made after the first open boll stage when treating dicamba-tolerant cotton. Therefore, the registrant should amend the product label to include this restriction since the data provided only support this pattern of use.

In regard to the Engenia Herbicide (EPA Reg. No. 7969-GUL), this end-use product is a new BAPMA salt formulation of dicamba developed by the BASF Corporation. It is an SL product proposed for use in treating conventional crops, as well as dicamba/glufosinate-tolerant cotton and dicamba-tolerant soybean. This end–use product contains 48.38% active ingredient in the form of the BAPMA salt of dicamba (equivalent to 5.0 lb ae/gal). The proposed BAPMA label depicts the same pattern of use found on the labels of the many other registered salts of dicamba which allows growers great flexibility for application to control weeds when cultivating crops. Table 3.3.2 provides a summary of the use directions taken directly from the proposed BAPMA product label.

| Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL). | | | | | | | |
|---|---|---|---|---|---|---|---|
| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
| *Asparagus* | | | | | | | |
| Post-emergence | 0.5 | NS[5] | 0.5 | NA[6] | 1 | 1 | |

**Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL).**

| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|
| Broadcast (40-60 gal/A) | | | | | | | - Apply in combination with glyphosate (Roundup).<br>- Do not harvest 24 hours after treatment.<br>- Do not use in the Coachella Valley of CA. |
| Post-harvest, Broadcast (Burndown Treatment) | 1.0 | | 2.0 | | | | |
| *Corn (field, seed, silage) and Popcorn* | | | | | | | |
| Preplant-Pre-emergence Broadcast | 0.5 | NS | 0.5 | 1.5 | 14 | NS | - Engenia is not registered on sweet corn.<br>- Do not contact seeds.<br>- Application rates vary by soil texture and growth stage.<br>- Adjuvants may be used and it can be mixed with other herbicide products. |
| Pre-emergence Broadcast | | | | | | | |
| Post-Emergence Broadcast | | | | | | | |
| *Cotton (non-dicamba-tolerant)* | | | | | | | |
| Pre-emergence Broadcast (Preplant Burndown) | 0.25 | NS | 0.25 | 0.25 | NA | NA | - Adjuvants may be used and it can be mixed with other herbicide products.<br>- After application, wait for 1" of rainfall/irrigation and a 21-day interval before planting.<br>- For MO and TN only, wait for 1" of rainfall/irrigation and a 14-day interval before planting. |
| *Cotton (dicamba/glufosinate-tolerant)* | | | | | | | |
| Pre-emergence Broadcast | 1.0 | NS | 1.0 | 2.0 | 14 | 7 | - Use of a COC or MSO adjuvants are only used when other products require them. For best results apply at min spray rate of 10 GPA. |
| Post-emergence, Broadcast | 0.5 | NS | 2.0 | | | | |
| *Grass Grown for Seed* | | | | | | | |
| Post-Emergence Broadcast | 1.0 | NS | 2.0 | NA | NS | 37-51 | - Apply with recommended adjuvants to seedling grasses when the crop reaches the 3-5 leaf stage.<br>- Follow listed grazing restrictions; 7 days for 0.5 lb ae/A applications |

**Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL).**

| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|
| | | | | | | | and 21 days for 1.0 lb ae/A applications.<br>- Follow listed PHI restrictions; 37 days for 0.5 lb ae/A applications and 51 days for 1.0 lb ae/A applications. |
| *Pasture, Hay, Rangeland, and Farmstead (non-cropland)* | | | | | | | |
| Broadcast treatment of non-cropland | 0.5 | NS | 1.0 | NA | NA | NA | - Engenia can be applied using water, oil-in-water emulsions including invert systems, or sprayable fluid fertilizer as a carrier.<br>- Follow listed grazing restrictions; 7 days for 0.5 lb ae/A applications and 21 days for 1.0 lb ae/A applications. |
| Broadcast treatment of small grain grown for pasture & newly seeded grass | 0.5 | | 0.5 | | | | |
| Spot Treatment | 0.001 - 5ft canopy 0.04 – 10 ft canopy 0.09 – 15ft canopy | | NS | | | | - Apply as a cut surface treatment for unwanted trees and prevention of sprouts of cut trees.<br>- Apply as an undiluted spot treatment directly to the soil or as a Lo-Oil basal bark treatment using an oil-in-water emulsion solution when plants are dormant. |
| *Proso Millet* | | | | | | | |
| Broadcast and spot treatment for broadleaf weed control | 0.125 | NS | 0.125 | NA | NS | NS | - Apply to actively growing weeds when proso millet is in the -2 to 5-leaf stage.<br>- Apply only if proso millet injury is acceptable.<br>- Follow listed grazing restrictions; 7 days for 0.5 lb ae/A. |
| *Small Grain (Barley, Oats, Triticale & Wheat)* | | | | | | | |

**Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL).**

| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|
| Post-emergence, Broadcast - Barley | 0.094 – up to 4-leaf stage | NS | 0.34 spring seeded barley | NA | NS | 7 and 37-hay | - May be applied before, during or after planting.<br>- Do not apply pre-harvest in CA.<br>- Do not use a COC for post-emergence application.<br>- Application in periods of rapid growth may result in temporary crop leaning.<br>- Do not apply if there potential for crop injury is unacceptable.<br>- Do not graze small grain within 7 days of treatment. |
| | | | 0.38 fall seeded barley | | | | |
| Post-emergence, Broadcast - Oats | 0.125 – up to 5-leaf stage | | 0.125 | | | | |
| Post-emergence, Broadcast – Wheat & Triticale | 0.125 – up to the 6-leaf stage | | 0.5 | | | | |
| Post-emergence, Broadcast – Fall Seeded Wheat | 0.25 – after the 3-leaf stage | | | | | | |
| *Sorghum* | | | | | | | |
| Pre-emergence Broadcast | 0.25 | NS | 0.5 | 0.5 | NS | 30 | - May be used pre-plant, post-emergence or pre-harvest in split applications.<br>- Pre-plant treatments are to be made 14-days before planting.<br>- Application in periods of rapid growth may result in temporary crop leaning.<br>- Do not graze before mature grain stage or within 7–days of treatment. |
| Post-emergence, Broadcast | | | | | | | |
| *Soybean (non-dicamba-tolerant)* | | | | | | | |
| Pre-plant Broadcast Spray | 0.25 @ a 14-day pre-plant Interval | NS | 0.5 | 2.0 | NS | 7 | - Application can be made with other herbicides.<br>- Pre-plant application cannot exceed 0.5 lbs ae/A per season. |
| | 0.5 @ a 28-day pre-plant Interval | | | | | | |

**Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL).**

| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|
| Pre-harvest Broadcast Spray | 1.0 | | 2.0 | | | | - Do not apply in areas where annual rainfall is below 25 inches.<br>- Pre-harvest applications are only made when pods are a mature brown color.<br>- Do not make pre-harvest applications in CA.<br>- Do not feed pre-harvest treated fodder and hay. |
| *Soybean (dicamba-tolerant)* | | | | | | | |
| Pre-emergence Broadcast | 1.0 | NS | 1.0 | 2.0 | NS | 7-forage And 14-hay | - Application can be made with other herbicides.<br>- Pre-emergent applications can be made at 1.0 lbs ae/A to medium to fine texture soils and at 0.5 lbs ae/A to course and sandy soils.<br>- Do not apply after first bloom.<br>- Post-emergent treatments may cause wilting for 24-72 hours afterwards.<br>- Do not apply post-emergent treatments by aerial application.<br>- Do not apply with ammonium containing additives. |
| Post-emergence, Broadcast | 0.5 | 2 | 1.0 | | | | |
| *Sugarcane* | | | | | | | |
| Post-emergence, Broadcast | 1.0 | NS | 2.0 | NA | NS | 87 | - Application can be made with other herbicides.<br>- Application may be made any time after weed emergence.<br>- When possible spray beneath the sugarcane canopy to minimize the likelihood of crop injury. |
| *Farmstead Turf (non-cropland) and Sod Farms* | | | | | | | |

**Table 3.3.2. Summary of Directions for Use of the Engenia 5.0 lb ae/gal SL Herbicide Formulation of Dicamba (EPA Reg. No. 7969-GUL).**

| Application. Timing, Type, and Equip. | Max. Applic. Rate (lb ae[1]/A) | Max. No. Applic. per Season | Max. Seasonal Applic. Rate (lb ae/A) | Combined Max. Seasonal Applic. Rate (lb ae/A) | RTI[2] (days) | PHI[3] (days) | Use Directions and Limitations[4] |
|---|---|---|---|---|---|---|---|
| Broadcast treatment | 0.5 | NS | 1.0 | NA | NS | NS | - To avoid injury to newly seeded grasses, delay application until after the second mowing.<br>- Application may cause stunting and discoloration in sensitive grasses (bentgrass, buffalograss, carpetgrass & St. Augustinegrass).<br>- Do not use on residential sites.<br>- Applications can be made at 0.25 lbs ae/A to medium to fine texture soils and at 0.125 lbs ae/A to course and sandy soils. |

[1] ae = Acid Equivalents
[2] RTI = Re-Treatment Interval
[3] PHI = Pre-Harvest Interval
[4] COC = Crop Oil Concentrate; MSO = Methylated Seed Oil.
[5] NS = Not Specified
[6] NA = Not Applicable

The proposed use directions for the new BAPMA salt formulation of dicamba are adequate to allow evaluation of the submitted bridging study data. The residue data provided examine the broad use pattern of dicamba using post-emergence broadcast treatments made at the maximum application rate following the specified minimum pre-harvest interval (PHI). Prior residue data submitted for dicamba-tolerant cotton shows that later post-emergence treatments give much higher residues then those made at earlier growth stages. Following the pattern of late season use demonstrated by the field trial data, no more than two (2) post-emergence applications may be made after the first open boll stage when treating dicamba-tolerant cotton. Therefore, the BAPMA product label must be amended to include this restriction since the data provided only support this pattern of use.

## 3.4 Anticipated Exposure Pathways

The Registration Division has requested an assessment of human health risk to support the proposed new use of dicamba on dicamba-resistant soybeans and cotton, and the proposed use of the BAPMA salt on various agricultural crops. Dicamba is currently registered for use on agricultural crops and for use on turf. Humans may be exposed to dicamba, including the counter ions of its various salt forms such as the BAPMA salt, in food and drinking water, since dicamba and BAPMA salt may be applied directly to growing crops and application may result in dicamba and BAPMA salt reaching surface and ground water sources of drinking water.

Additionally, humans may be exposed to the plant metabolite, DCSA, via dietary exposures. There are residential uses of dicamba, but not the dicamba BAPMA salt. Adults may be exposed to dicamba during pesticide applications in residential settings, and both adults and children may be exposed dermally in post-application scenarios on turf. Children may also have incidental oral exposure in post-application scenarios for turf to dicamba acid. Non-occupational exposures from spray drift may occur from both dicamba acid and the BAPMA salt. In an occupational setting, applicators may be exposed during application of dicamba acid and the BAPMA salt. There is a potential for post-application exposure for workers re-entering treated fields.

Risk assessments have been previously prepared for the existing uses of dicamba. This risk assessment considers all of the aforementioned exposure pathways based on the proposed new uses of dicamba, including the counter ions of its various salt forms such as the BAPMA salt, but also considers the existing uses as well, particularly for the dietary exposure assessment. There are several compounds that have been considered, including dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the dicamba BAPMA counter ion. Separate assessments of dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the BAPMA counter ion were not needed because the selected endpoints are protective of all forms.

## 3.5 Consideration of Environmental Justice

Potential areas of environmental justice concerns, to the extent possible, were considered in this human health risk assessment, in accordance with U.S. Executive Order 12898, "Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations," (http://www.archives.gov/federal-register/executive-orders/pdf/12898.pdf). As a part of every pesticide risk assessment, OPP considers a large variety of consumer subgroups according to well-established procedures. In line with OPP policy, HED estimates risks to population subgroups from pesticide exposures that are based on patterns of that subgroup's food and water consumption, and activities in and around the home that involve pesticide use in a residential setting. Extensive data on food consumption patterns are data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA) and are used in pesticide risk assessments for all registered food uses of a pesticide. These data are analyzed and categorized by subgroups based on age, season of the year, ethnic group, and region of the country. Additionally, OPP is able to assess dietary exposure to smaller, specialized subgroups and exposure assessments are performed when conditions or circumstances warrant. Whenever appropriate, non-dietary exposures based on home use of pesticide products and associated risks for adult applicators and for toddlers, youths, and adults entering or playing on treated areas post-application are evaluated. Further considerations are currently in development as OPP has committed resources and expertise to the development of specialized software and models that consider exposure to bystanders and farm workers as well as lifestyle and traditional dietary patterns among specific sub-groups.

# 4.0 Hazard Characterization and Dose-Response Assessment

Dicamba (3, 6-dichloro-2-methoxybenzoic acid) is a selective benzoic acid herbicide registered for controlling a wide variety of broadleaf weeds and woody plants prior to their emergence for

conventional crops. It is an auxin agonist and has similar signaling properties to natural plant auxins, which induce abnormal and uncontrollable growth to disrupt normal plant functions at high concentrations. The pesticidal mode of action of dicamba is not known to be relevant to mammals. Dicamba-tolerant plants convert dicamba into the non-herbicidal metabolite 3, 6-dichlorosalicylic acid (DCSA), thus causing the plant to tolerate the herbicidal effect of dicamba for post-emergence applications.

## 4.1 Toxicology Studies Available for Analysis

The toxicology database on dicamba is extensive and complete with respect to 870 guideline requirements for characterizing the hazard of dicamba, with routes of administration that are consistent with potential exposure scenarios. The toxicology studies for dicamba acid, its salts [isopropylamine (IPA) and diglycolamine (DGA)], the currently proposed N, N-Bis-(3-aminopropyl) methylamine (BAPMA) salt, and the plant metabolites DCSA (3, 6-dichlorosalicylic acid) and DCGA (3, 6-dichlorogentisic acid) are summarized in Appendix A. The data from the following studies were used to evaluate the hazard potential of dicamba acid and dicamba BAPMA salt:

Dicamba Acid, IPA and DGA Salts:
Sub-chronic Oral Study: 90-day oral toxicity (rat),
Dermal Studies: 28-day dermal toxicity (rat), 21-day dermal toxicity (rabbit)
Developmental Studies: rat and rabbit developmental toxicity studies
Reproduction Study: 2-generation reproduction study (rat)
Chronic Studies: combined oral chronic toxicity/carcinogenicity (rat), carcinogenicity (mouse), chronic oral toxicity (dog)
Neurotoxicity Studies: acute and subchronic neurotoxicity (rat)
Inhalation Study: 28-day inhalation study (rat)
Immunotoxicity Study: Immunotoxicity (rat)
Mutagenicity battery
Metabolism

DCSA Metabolite:
Subchronic Studies: 90-day oral toxicity (rat), 90-day oral toxicity (dog)
Developmental Studies: rat and rabbit developmental toxicity studies
Reproduction Study: 2-generation reproduction study (rat)
Chronic Study: combined oral chronic toxicity/carcinogenicity (rat)
Mutagenicity battery
Metabolism

DCGA Metabolite:
Sub-chronic Study: 28-day oral toxicity (rat)
Mutagenicity battery

Dicamba BAPMA Salt
Inhalation Study: 28-day inhalation study (rat)
90-Day Oral Study in Rats

Developmental Study (rat)
Mutagenicity battery

BAPMA Cation Base
OECD 422 Reproduction/Developmental Study

## 4.2 Absorption, Distribution, Metabolism, & Elimination (ADME)

The metabolism study in rats showed that following oral gavage administration at 400 mg/kg, dicamba is rapidly absorbed within a few hours and rapidly excreted. The phase I plasma half-life is less than 4 hours at doses of 400 mg/kg or lower and essentially all of the radio-labelled dicamba is eliminated in 48 hours. Over 95% of the administered dose is excreted in the urine. The compound is not metabolized nor accumulated by the tissues in adult, non-pregnant rats. However, approximately 13% of dicamba in the urine is conjugated as the glucuronide. In plants, dicamba is converted to the DCSA and DCGA metabolites, which have dietary exposures.

The gavage plasma pharmacokinetic studies in rats showed that absorption of radiolabeled dicamba was rapid, with peak plasma concentrations found within 2 hours of treatment. Absorption was not saturated, even at the highest dose (800 mg/kg), as indicated by increasing plasma concentrations with doses. However, the increase in plasma concentration was non-linear/disproportionate from one dose to the next dose and serum half-life increased with dose, which is consistent with saturation of excretion. Another plasma pharmacokinetic study suggests that dicamba is an inhibitor of renal anion transport (i.e. urinary excretion) since co-dosing with an inhibitor of this process (i.e. probenecid) increased plasma levels of dicamba and decreased its clearance rate. No significant treatment-related differences between the genders were found. A DCSA study demonstrates that DCSA has a similar structure and metabolism as dicamba, with rapid absorption and rapid elimination. DCSA is poorly metabolized (except for some glucuronide conjugates) and predominantly excreted in the urine as the parent compound.

### 4.2.1 Dermal Absorption

An acceptable guideline dermal absorption study is not available for dicamba. The lack of a dermal absorption study is not a concern since quantification of dermal risk is not required due to lack of dermal or systemic toxicity at the limit dose (1000 mg/kg/day) following repeated application to rats and/or rabbits with the dicamba acid and the IPA and DGA salts.

## 4.3 Toxicological Effects

Reviewing the various toxicity studies on the different forms of dicamba acid, BAPMA salt, and DCSA plant metabolite, it appears that the mode of administration (i.e. gavage vs. dietary) had an impact on the type of toxicity observed for these compounds. For example, the repeat dietary administration have effects occurring at higher doses than the acute gavage dosing. Following gavage administration, there were rapid onset of clinical signs as seen in the metabolism study at lower doses in the gavage studies. The dicamba acid and dicamba BAPMA studies indicate that the nervous system is the major target following gavage exposure. These clinical signs include ataxia, decreased foot splay, decreased arousal and rears/minutes and decreased motor activity.

For dicamba acid and the BAPMA salt, signs consistent with neurotoxicity were observed in several gavage studies in rats and rabbits without accompanying histopathology. For dicamba acid, when comparing the gavage acute neurotoxicity (ACN) study with the dietary sub-chronic neurotoxicity (SCN) study, the acute effect level was over 2.5X lower than the subchronic effect level for the same endpoints of rigidity and impaired gait and impaired righting reflex. The DCSA metabolite is less neurotoxic than dicamba acid. For DCSA, clinical signs were only evident at gavage doses of 1000 mg/kg or greater in the mouse micronucleus study (hypo-activity, squinted eyes, hunched posture) or the rat acute oral toxicity study at 2000 mg/kg (wobbly gait), while clinical signs for dicamba acid (hypo-activity, ataxia) were apparent at gavage doses of 250 mg/kg or greater in the mouse micronucleus assay. DCSA caused decreased body weight and increased creatinine levels (a measure of renal deficiency) in the rat 90-day dietary study at 659 mg/kg/day. DCSA produced decreased body weight, emesis, and an increase in clotting time in the dog sub-chronic 90-day oral study only at the highest doses tested (HDT, capsule, 150 mg/kg/day). Dicamba BAPMA caused increased clotting time and increased creatinine levels in the rat 90-day dietary study at the limit dose. However in the gavage rat developmental study, dicamba BAPMA caused ataxia, unsteady gait and convulsions at 86 mg/kg/day. The creatinine effects, along with the pharmacokinetics/excretion data, suggests that the kidney is also a target organ and that adverse effects begin to occur at doses where kidney clearance starts to become non-linear. There was no evidence of immunotoxicity with the acid form.

Pre-natal developmental gavage toxicity studies in rats and rabbits, and two-generation reproduction studies in rats were available with the dicamba acid and the DCSA plant metabolite. The developmental studies in rats and rabbits showed no evidence (qualitative or quantitative) for increased susceptibility following *in utero* exposure of dicamba acid or the dicamba BAPMA salt. In the rat developmental studies for dicamba acid or dicamba BAPMA, there was no developmental toxicity up to the highest dose tested, but the BAPMA salt was approximately 4 times more toxic to the dams than dicamba acid based on the common effect of ataxia. A single incidence of abortion in the dicamba rabbit developmental toxicity study (1 in 20 does, 4 days after dosing ceased) occurred at a maternally toxic dose (manifested as ataxia and decreased motor activity). For the DCSA metabolite, there was no developmental toxicity up to the highest doses tested in the definitive studies in rats and rabbits. At higher doses in the DCSA developmental range-finding studies, there were decreased fetal weights in rats at the same dose that caused rales in the dams and dam deaths occurred at the highest dose tested in rabbits. In the OECD 422 reproduction/developmental screening study (870.3650) with the BAPMA base, decreased motor activity and water consumption were observed in dams at the mid dose while pronounced toxicity and deaths were observed in the dams at the highest dose tested (HDT). This OECD 422 study did not identify developmental toxicity. However, dicamba product exposure is not to the pure BAPMA base and the base composition in the dicamba BAPMA salt is only one-fourth that of the dicamba component in this salt form. Thus, the dicamba BAPMA salt rat developmental study PODs will be protective for the BAPMA base effects.

In contrast, following pre and/or post-natal exposures in the two-generation reproduction studies, the DCSA metabolite was more toxic to the offspring than the acid form. In the reproduction study with DCSA, offspring toxicity manifested as decreases in body weight at a dose (37 mg/kg/day) that is approximately10-fold lower than the dose (362 mg/kg/day) that caused

parental/systemic toxicity (decreased body weight) demonstrating increased susceptibility in the young. Furthermore, when the adverse effects observed in the offspring were compared for the two compounds (*i.e.* LOAEL comparison), the DCSA dose (37 mg/kg/day) at which decreased pup weight was observed was approximately 12-fold lower than the dicamba acid dose (450 mg/kg/day) that caused the same effect.

Conversely, in the reproduction study with dicamba acid there was no evidence (qualitative or quantitative) for increased susceptibility following *pre and/or* or postnatal exposure. Decreased pup body weights were observed in all generations and matings at the mid (136 mg/kg/day) (86 - 90% of control) and at the high (450 mg/kg/day) (74 - 94% of control) dose groups throughout lactation, relative to the concurrent controls. Based on detailed statistical analysis (multivariate) comparison with the MARTA historical control data (Middle-Atlantic Reproduction and Teratology Association, Appendix 6), it was concluded that there was no adverse effect on pup body weights during the F1 generation lactation period or post-weaning phase at the low and mid dose groups. The offspring NOAEL was established at 136 mg/kg/day and the offspring LOAEL was 450 mg/kg/day based on decreased pup weights in the F1 and F2B generations. At the 450 mg/kg/day dose, there were adverse decreases in the F1 pup body weights at PND 0 before the lactation phase.

In the dicamba acid, dicamba IPA and dicamba DGA salts sub-chronic dermal toxicity studies, there were no adverse effects observed up to the limit dose (1000 mg/kg/day). However, the dicamba BAPMA salt was demonstrated to be more toxic than dicamba acid via the inhalation route. The inhalation study for dicamba acid revealed hyperplasia in the lung with a clear no observed adverse effect level (NOAEL), while the dicamba BAPMA salt produced hyperplasia and ulceration of the larynx at a dose approximately 35 times lower than dicamba acid effects and a NOAEL was not established. The inhalation effects for both dicamba acid and the BAPMA salt were local and non-systemic.

Dicamba is classified as "not likely to be carcinogenic to humans" based on the lack of evidence of carcinogenicity in mice and rats with the acid form and in rats with DCSA. Mutagenicity studies generally did not demonstrate evidence of mutagenic potential for dicamba although some positive results were reported *in vitro*. Dicamba acid and the dicamba BAPMA salt both induced chromosomal aberrations in human lymphocytes *in vitro*, however, genotoxicity was negative *in vivo* in the mouse micronucleus assay, thus the concern for genotoxicity for dicamba or its salts is low. The BAPMA base was negative for genotoxicity in bacteria, but positive for genotoxicity based on in *vitro* mammalian cell culture.

Dicamba acid has a low acute toxicity via oral, dermal and inhalation route (Acute Toxicity Categories III or IV). It is an eye and dermal irritant but it is not a skin sensitizer. BAPMA base is Category II or III toxicity via oral, dermal or inhalation routes, but it is corrosive to the eyes and a dermal irritant and sensitizer. The dicamba BAPMA salt has a low acute toxicity via oral, dermal or inhalation route (Acute Toxicity Categories III or IV). The dicamba BAPMA salt is not an eye or dermal irritant, but it is a skin sensitizer.

## 4.4 Safety Factor for Infants and Children (FQPA Safety Factor)

The FQPA Safety Factor (SF) may be reduced (i.e. 1X) for acute and chronic dietary risk assessments for the following reasons:

1. The toxicity database for dicamba is complete with respect to required 870 guideline studies.
2. For the dicamba acid, there is no evidence of increased susceptibility following *in utero* exposures to rats and rabbits and following pre and/or post-natal exposure to rats in a two-generation reproduction study. For the dicamba acid and BAPMA salt, no developmental toxicity was seen at the highest doses tested in the prenatal developmental studies with rats. Although quantitative offspring susceptibility was observed in the 2-generation reproduction study for the DCSA metabolite based on decreased pup weights, the degree of concern for the susceptibility is low because there is a well-established NOAEL for offspring toxicity in that study and DCSA has rapid clearance. Additionally, the current points of departure are health protective and therefore address the concern for offspring toxicity observed in this reproduction study.
3. Consistent neurotoxic signs (e.g., ataxia, decreased motor activity, impaired righting reflex and gait) were observed in multiple studies in rats and rabbits. After considering the available toxicity data, EPA determined that there is no need for a developmental neurotoxicity study or additional UFs to account for neurotoxicity for the following reasons: (1) although clinical signs of neurotoxicity were seen in pregnant animals, no evidence of developmental anomalies of the fetal nervous system were observed in the prenatal developmental toxicity studies, in either rats or rabbits, at maternally toxic doses up to 300 or 400 mg/kg/day, respectively; (2) there was no evidence of behavioral or neurological effects on the offspring in the two-generation reproduction study in rats; (3) the ventricular dilation of the brain in the combined chronic toxicity and carcinogenicity study in rats was only observed in females at the high dose after two years of exposure at doses of 127 mg/kg/day. The significance of this observation is questionable, since no similar histopathological finding was seen in two sub-chronic neurotoxicity study at the limit dose or other chronic studies.
4. There are no residual uncertainties identified in the exposure databases. The dietary food exposure assessments were performed based on tolerance-level residues for the acute dietary, average field trial data for the chronic dietary and available % crop-treated information. Conservative ground and surface water modeling estimates were used. Similarly, conservative residential SOPs were used to assess post-application exposure of children as well as incidental oral exposure of toddlers. These assessments will not under-estimate the exposure and risks posed by dicamba.

However, the 10X FQPA SF is retained for assessing inhalation risks for the dicamba BAPMA salt, the FQPA SF is retained in the form of a LOAEL to NOAEL factor ($UF_L$) since the POD used was a LOAEL (See Table 4.5.4.1).

### 4.4.1 Completeness of the Toxicology Database

The toxicity database for dicamba is adequate in terms of endpoint selection and dose response information to characterize the potential for dietary prenatal or postnatal risk to infants and

children. Available studies include acceptable rat and rabbit developmental toxicity studies, two rat 2-generation reproduction studies, and acute/subchronic neurotoxicity studies in rats.

### 4.4.2 Evidence of Neurotoxicity

There is evidence of neurotoxicity resulting from exposure to dicamba throughout the toxicology database (i.e. impaired gait, impaired righting reflex, ataxia, decreased motor activity, rigidity upon handling, etc). After considering the available toxicity data, the agency determined that a DNT is not required, as described previously.

### 4.4.3 Evidence of Sensitivity/Susceptibility in the Developing or Young Animal

There is no evidence of susceptibility to the young following *in utero* exposure to dicamba acid, dicamba BAPMA or DCSA. However, quantitative offspring susceptibility was observed in the 2-generation reproduction study for the DCSA metabolite based on decreased pup weights. The degree of concern for the susceptibility is low because there is a well-established NOAEL for offspring toxicity in that study and DCSA has rapid clearance. Additionally, the current point of departures are health protective and therefore address the concern for offspring toxicity observed in the reproduction studies.

### 4.4.4 Residual Uncertainty in the Exposure Database

The residential exposure assessment assumes maximum label use rate as well as other conservative assumptions. The acute dietary exposure assessment is based on an exaggerated exposure scenario which assumes that all commodities being consumed retain tolerance level residues. The drinking water estimates utilized conservative models. Therefore, the Agency does not believe that exposure to dicamba will be under-estimated.

## 4.5 Toxicity Endpoint and Point of Departure Selections

The toxicology endpoints and points of departure selections have been updated since the last risk assessment (D340156, 2008) to consider new toxicology data for the dicamba BAPMA salt, as well as the route-specific inhalation study results for dicamba acid (see Appendix A.3).

### 4.5.1 Dose-Response Assessment

Dicamba acid has dietary, dermal, inhalation and incidental oral exposure scenarios. The dicamba BAPMA salt has no residential uses, thus there is no incidental oral exposures. The DCSA metabolite is not formed in mammals and is generated within plants, thus its main exposure is for chronic dietary scenarios. The DCSA reproduction study POD was not selected for non-dietary endpoints, since the residue present on foliar surfaces to which people may be exposed is the parent compound rather than the DCSA metabolite. The detailed description of the toxicity studies used for selecting toxicity endpoints and points of departure for various exposure scenarios are presented in appendix A.

*Acute Dietary Scenarios:* The rat developmental study for the dicamba BAPMA salt was selected to assess a single oral exposure of the general population, including infants and children, to dicamba acid or its BAPMA salt. The NOAEL is 29 mg/kg/day, and the LOAEL is 86 mg/kg/day based on ataxia, unsteady gait and convulsions in the dams (considered a single-dose effect since the signs occurred within 3 hours after dosing). This study was selected because it represents the most sensitive endpoint in the dicamba database for exposure to the parent dicamba acid or its BAPMA salt demonstrating an acute response with a well-defined NOAEL value. The decreases in the pup body weights in the reproduction studies are not considered single dose effects. The selected POD will be protective of the effects of dicamba acid and the BAPMA salt via the oral route. A separate acute dietary assessment for females 13-49 was not performed since no there was no developmental toxicity attributed to a single dose in the toxicology data base. The single incidence of abortion in the rabbit developmental study occurred late gestation and therefore likely not from a single exposure.

An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain an acute RfD of 0.29 mg/kg/day. Since the FQPA SF is reduced, the acute Population Adjusted Dose (PAD) is equivalent to the acute RfD (0.29 mg/kg/day).

*Chronic Dietary Scenarios:* The chronic dietary scenario for dicamba acid and all of its salt forms is based on decreased pup weights observed at 37 mg/kg/day (LOAEL) in a reproduction study on the DCSA plant metabolite; the NOAEL of 4 mg/kg/day is selected for deriving the chronic RfD. This POD will be the most protective of all toxic effects seen following exposure to dicamba acid or dicamba BAPMA salt. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain a chronic RfD of 0.04 mg/kg/day. Since the FQPA SF was reduced, the chronic PAD is equivalent to cRfD (0.04 mg/kg/day).

*Short and Intermediate Term Incidental Oral Scenarios:* The toxicology studies on the plant metabolites are not appropriate for this scenario since these metabolites are generated inside the plants and unavailable for incidental oral exposure. The developmental studies are not appropriate for incidental oral scenarios involving hand-to-mouth behavior. The dicamba BAPMA salt has no residential uses other than potential for spray drift. The most appropriate study was the multi-generation reproductive toxicity study in rats dosed with parent compound was selected based on impaired pup growth at 450 mg/kg/day (LOAEL); the NOAEL of 136 mg/kg/day was selected as the POD for this scenario. The Level of Concern (LOC) is a Margin of Exposure (MOE) of 100 which includes the 10X factor accounts for interspecies extrapolation, a 10X factor accounts for intraspecies variation, and a 1X FQPA SF.

*Short, Intermediate and Long-Term Inhalation Scenarios:* The dose and endpoint selected for dicamba acid and dicamba BAPMA risk assessment utilized the route-specific aerosol inhalation studies for each AI. For dicamba acid inhalation risk assessment for short and intermediate term durations, the POD was based on the route-specific dicamba acid inhalation toxicity study in Wistar rats with a LOAEL of 0.050 mg/L based on local effects of hyperplasia in the lungs and lymph nodes (NOAEL = 0.005 mg/L, non-systemic, pulmonary RDDR = 0.590).

The dose and endpoint selected for the dicamba BAPMA salt inhalation risk assessment for short and intermediate term durations were based on the dicamba BAPMA salt inhalation toxicity study in rats with a LOAEL of 0.0014 mg/L based on local effects of hyperplasia and ulceration of the larynx (no NOAEL, non-systemic, extra-thoracic RDDR = 0.190).

The standard interspecies extrapolation UF can be reduced from 10X to 3X for dicamba acid and BAPMA salt due to the calculation of human equivalent concentrations (HECs) accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. Therefore, the LOC for dicamba acid inhalation exposures is for MOEs less than 30 (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF when applicable). For BAPMA salt, an additional 10X $UF_L$ is applied due to lack of a NOAEL; therefore, the LOC for BAPMA salt inhalation exposures is for MOEs less than 300. The inhalation HEC/HED results are listed in Appendix A.5.

*Short, Intermediate, and Long-term Dermal Scenarios:* A dermal assessment is not required for dicamba acid or its BAPMA salt since no effects were detected up to the limit dose (1000 mg/kg/day) in the dermal studies for dicamba acid, IPA salt and DGA salt. Additionally, the dicamba anion is the major component in the BAPMA salt and the BAPMA base component of the dicamba BAPMA salt is only 20% of the salt mass (and 28% on a molar basis), thus, the dicamba BAPMA salt is unlikely to have adverse dermal effects. In support, the acute dermal toxicity for the dicamba BAPMA salt is low (Category IV).

The BAPMA amine base does not require a separate assessment since the OCED 422 developmental/reproduction toxicity screening study on the pure compound had a LOAEL of 100 mg/kg/day based on decreased motor activity and water consumption with a NOAEL of 25 mg/kg/day. Thus, the dicamba BAPMA rat developmental study will be protective for its exposure and considering the BAPMA composition in this salt is 4 times less than the dicamba acid composition. Furthermore, the BAPMA cation is predicted to degrade much faster than the dicamba anion.

### 4.5.2 Recommendation for Combining Routes of Exposures for Risk Assessment

Based upon different toxicological effects and/or target organs observed in the selected endpoints for risk assessment, incidental oral, dermal, and inhalation routes of exposure should not be combined for dicamba acid or dicamba BAPMA salt. Therefore, the dicamba salt weights will be utilized for regulation, not the dicamba acid equivalents.

### 4.5.3 Cancer Classification and Risk Assessment Recommendation

In accordance with the EPA Final Guidelines for Carcinogen Risk Assessment (March 29, 2005), dicamba is classified as "not likely to be carcinogenic to humans". This decision was based on the lack of findings in the cancer studies in rats and mice which were tested at adequate dose levels to assess the carcinogenicity of dicamba (TXR No. 0053647). Mutagenicity studies generally did not demonstrate evidence of mutagenic potential for dicamba although some positive results were reported *in vitro*. Dicamba acid and the dicamba BAPMA salt both induced

chromosomal aberrations in human lymphocytes *in vitro*, however, genotoxicity was negative *in vivo* in the mouse micronucleus assay, thus the concern for genotoxicity for dicamba or its salts is low. The BAPMA base was negative for genotoxicity in bacteria, but positive for genotoxicity based on in *vitro* mammalian cell culture. Additionally, the DCSA metabolite also had a lack of findings in a chronic/carcinogenicity study in rats.

### 4.5.4 Summary of Points of Departure and Toxicity Endpoints Used in Human Risk Assessment

**Table 4.5.4.1 Toxicological Doses and Endpoints for Dicamba Acid and Dicamba BAPMA Salt for use in Human Health Risk Assessments**

| Exposure Scenario | Point of Departure | FQPA SF and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Acute Dietary (General population including infants and children) | NOAEL = 29 mg/kg/day | $UF_A$ =10X<br>$UF_H$ =10X<br>FQPA SF = 1X<br><br>Acute RfD = 0.29 mg/kg/day<br>aPAD = 0.29 mg/kg/day | **Dicamba BAPMA**<br>**Rat Developmental Study**<br><br>**Maternal**<br>NOAEL is 29 mg/kg/day in dams<br>LOAEL is 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions observed shortly after dosing<br><br>**Developmental**<br>NOAEL > 288 mg/kg/day<br>(200 mg/kg/day as acid equivalent) |
| Acute Dietary (Females 13-49 years of age) | N/A | N/A | No developmental toxicity attributed to acute exposure in the toxicology database. The abortions in the rabbit developmental study occurred at gestation day 22. |
| Chronic Dietary (All populations) | Offspring NOAEL= 4 mg/kg/day | $UF_A$ =10X<br>$UF_H$ =10X<br>FQPA SF = 1X<br><br>Chronic RfD = 0.04 mg/kg/day<br>cPAD = 0.04 mg/kg/day | **Reproductive study in rats with <u>DCSA metabolite.</u>**<br><br>Offspring LOAEL = 37 mg/kg/day based on decreased pup weights in F1 generation on PND 14 and 21 (both sexes) and week 18 (females) |
| Short- (1 - 30 Days) and Intermediate- (1-6 months) Term Incidental Oral | Offspring NOAEL= 136 mg/kg/day | Residential<br>LOC for MOE = 100<br><br>$UF_A$ =10X<br>$UF_H$ =10X<br>FQPA SF = 1X | **Reproductive study in rats with <u>Dicamba Acid</u>.**<br><br>Offspring LOAEL=450 mg/kg/day based on decreased pup weights. |
| No dermal assessment for dicamba acid since the dermal toxicology studies for dicamba acid, IPA and DGA salts all had NOAELs of 1000 mg/kg/day. | | | |

**Table 4.5.4.1 Toxicological Doses and Endpoints for Dicamba Acid and Dicamba BAPMA Salt for use in Human Health Risk Assessments**

| Exposure Scenario | Point of Departure | FQPA SF and Level of Concern for Risk Assessment | Study and Toxicological Effects |
|---|---|---|---|
| Dicamba Acid<br>Short-, Intermediate- and Long-Term Inhalation | NOAEL=0.005/0.005 mg/L (M/F)<br><br>Residential Handler<br>HED=0.07 mg/kg/day<br>HEC=0.00295 mg/L<br>Residential Bystander<br>HEC=0.00053 mg/L<br>Occupational Handler<br>HED=0.21 mg/kg/day<br>HEC=0.00221 mg/L | Residential<br>LOC for MOE = 30<br><br>Occupational<br>LOC for MOE = 30<br><br>$UF_A$ = 3X<br>$UF_H$ =10X<br><br>FQPA SF = 1X | **Aerosol inhalation study in rats with Dicamba Acid.**<br><br>NOAEL=0.005/0.005 mg/L (M/F)<br>LOAEL=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females |
| Dicamba BAPMA Salt<br>Short-, Intermediate- and Long-Term Inhalation | LOAEL = 0.0014 mg/L<br><br>Occupational Handler<br>HED=0.020 mg/kg/day<br>HEC=0.0002 mg/L<br><br>Residential Bystander<br>HEC=0.00005 mg/L | Residential<br>LOC for MOE = 300<br><br>Occupational<br>LOC for MOE = 300<br><br>$UF_A$ = 3X<br>$UF_H$ =10X<br><br>$UF_L$ = 10X | **Dicamba BAPMA**<br>**Rat Inhalation Study**<br><br>NOAEL=NA<br>LOAEL=0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia in the larynx |
| Cancer<br>(Oral, dermal, inhalation) | Dicamba is classified as "not likely to be carcinogenic to humans". | | |

Point of Departure (POD) = A data point or an estimated point that is derived from observed dose-response data and used to mark the beginning of extrapolation to determine risk associated with lower environmentally relevant human exposures. NOAEL = no observed adverse effect level. LOAEL = lowest observed adverse effect level. UF = uncertainty factor. $UF_A$ = extrapolation from animal to human (interspecies). $UF_H$ = potential variation in sensitivity among members of the human population (intraspecies). $UF_L$ = use of a LOAEL to extrapolate a NOAEL. $UF_S$ = use of a short-term study for long-term risk assessment. FQPA SF = FQPA Safety Factor. PAD = population adjusted dose (a = acute, c = chronic). RfD = reference dose. MOE = margin of exposure. LOC = level of concern. N/A = not applicable.

## 4.6 Public Health, Incidents and Epidemiology Information

The incident review identified a relatively high frequency of cases reported for dicamba in both the Incidents Data System (IDS) and SENSOR-Pesticides (Evans, S. and Recore, S., D427231). While the majority of case reports are low in severity in both databases, there are a number of moderate severity cases reported and further review of dicamba may be warranted.

The Agricultural Health Study (AHS) includes dicamba and the study authors conclude that there were not significant associations with cancer overall or strong associations with any specific type of cancer.

### 4.6.1 Incidents

For the Main IDS, from January 1, 2010 to May 27, 2015, there were 309 incidents reported involving dicamba. Fourteen of these incidents were classified as major severity, 292 incidents

were classified as moderate severity, three were classified as minor severity, and two were classified as having no or unknown effects.

In Aggregate IDS, from January 1, 2010 to May 27, 2015, there were 2032 incident reported involving dicamba. Forty one incidents were classified as having no or unknown effects and 1991 incidents were classified as minor severity. Minor severity means that a person alleged or exhibited some symptoms, but they were minimally traumatic, the symptoms resolved rapidly and usually involved skin, eye or respiratory irritation.

The top five implicated dicamba products in IDS are all products for use by homeowners to treat lawns. These products are all co-formulated with additional active ingredients. Four of these products are ready to use formulations and the other two are soluble concentrate formulations that can be used with a hose-end sprayer or a tank sprayer.

A query of SENSOR-Pesticides 1998-2011 identifies 290 cases, stemming from 270 events, involving dicamba. Six cases are single ai products and the remaining 284 cases are multiple ai products.

A total of 252 cases were low in severity, 36 cases were moderate in severity, and two cases were high severity. Both of the high severity incidents involved intentional ingestion for self-harm and will not be further analyzed.

The majority of cases were non-occupational (62%) and occurred in private residences (51%). 41% of cases were applying the product at the time of exposure and another 40% of cases were residential bystanders, such as family members, who were in the residence during or after the application at the time of the exposure. Occupational cases comprise 28% of total case reports, including half of the moderate severity cases.

Symptoms most commonly reported for dicamba cases involved the nervous system (n=144), primarily headache and dizziness; the respiratory system (n=125), primarily upper respiratory pain and shortness of breath, followed by gastrointestinal system (n=117) and dermatological system (n=109).

Cases occurred in a variety of settings, with 179 cases were not work-related (residential), 80 cases were work-related, and 31 cases had unknown work status. Most cases (n=150) occurred in private residences and 50 cases occurred on a farm. Nine cases, stemming from four events, occurred at schools.

### 4.6.2 Epidemiology Data

In an AHS paper entitled "Cancer Incidence among Pesticide Applicators Exposed to Dicamba in the Agricultural Health Study" authors found no strong association between dicamba exposure and cancer risk. (Samanic, et al. 2006). In this study, Samanic et al. incorporated incident cancers diagnosed between enrollment (generally between 1993 and 1997) and December 31, 2002 by linkage to state cancer registries. Poisson regression was used to estimate rate ratios and

associated confidence intervals by tertiles of dicamba exposure. The authors concluded that "Exposure was not associated with overall cancer incidence nor were there strong associations with any specific type of cancer". More specifically, no statistically significant associations were seen using intensity-weighted lifetime exposure days and the "No exposure" group as a referent category. While a trend was apparent *(p = 0.02),* none of the individual point estimates was significantly elevated and the authors state that this result is due largely due to elevated risk at the highest exposure level.

## 5.0 Dietary Exposure and Risk Assessment

## 5.1 Metabolite/Degradate Residue Profile

### 5.1.1 Summary of Plant and Animal Metabolism Studies

Tier II summary review section 6.2.1 "Metabolism, distribution and expression of residues in plants"
Reregistration Eligibility Decision Memo, D317699, 12/20/2005, C. L. Olinger
Residue Chemistry Summary, D408384, A. Kamel, 4/18/2013
48728701.der, P. Savoia, 03/25/2013 (or Residue Chemistry Summary)

For non-dicamba-resistant plants, the nature of the residue was previously determined to be understood (D317699, C. L. Olinger, 12/20/2005). Prior plant metabolism studies were reviewed in part with the 1983 residue chemistry chapter of the dicamba registration standard. The studies demonstrate that dicamba is rapidly absorbed and translocated by grasses, grapes, black valentine beans, wheat and bluegrass, as well as in soybeans. Dicamba is metabolized in plants mainly by demethylation and hydroxylation.

A new metabolism study submitted by the registrant on dicamba resistant soybean shows that the identified dicamba metabolites were DCSA glucoside (60.32-74.48% of TRR), which was the major component in dicamba-tolerant soybean, DCSA HMGglucoside (1.14-7.62% of TRR), DCGA glucoside (0.75-4.32%), DCGA malonylglucoside (0.73-5.46% of TRR), DCSA (1.54-4.08% of TRR), in addition to two minor un-identified metabolites characterized as mixtures of unknown DCSA and DCGA conjugates, each constituted less than 2.0% of the TRR. The metabolite 5-OH dicamba, which is part of the current tolerance expression, has not been detected.

The petitioner has also submitted a new metabolism study for dicamba-tolerant cotton (48728701.der, P. Savoia, 03/25/2013). Metabolism was found to occur at an appreciable rate with the first step in the process being demethylation of parent into the DCSA metabolite. Residue levels were considerably lower for the pre-emergence samples in comparison to those obtained following post-emergence treatment. Parent dicamba was identified in all the matrices tested which include both gin byproducts and in seed at lower levels. Its metabolites DCSA glucoside, DCSA, and DCGA glucoside were found to be present in all matrices as well. The 5-OH dicamba metabolite was not identified in any matrix. For dicamba-tolerant cotton, DCSA glucoside was the major metabolite obtained with the highest levels being found in the gin byproducts samples.

The nature of dicamba residues in animals was previously determined based on acceptable metabolism studies conducted on ruminants and poultry (MRID 43245201-2). The residues of

concern in meat, milk, poultry and eggs consisted of dicamba and 3,6-dichloro-2-hydroxybenzoic acid (DCSA) [40 CFR §180.227 (a)(2)].

The nature of the dicamba residue in rotational crops was previously reviewed. It has been concluded that limited and/or extensive field accumulation studies with dicamba were not necessary and rotational crop tolerances need not be established provided the registrants amended all dicamba labels to specify a 120-day plant-back interval (PBI) when dicamba is applied at a maximum seasonal rate of 0.75 lb ae/A or less. At application rates of 0.75-2.0 lb ae/A, only crops with established tolerances can be rotated for planting.

### 5.1.2 Summary of Environmental Degradation

Dicamba is very soluble in water (6100 ppm) and very mobile ($K_{oc}$ = 13.4) in the laboratory. Because dicamba is not persistent under aerobic conditions, very little dicamba could be expected to leach to groundwater. If any dicamba did reach anaerobic ground water, it would be somewhat persistent (due to its anaerobic half-life of 141 days); any DCSA that reached ground water would be expected to persist. Results from two acceptable field dissipation studies conducted with dimethylamine salt of dicamba, indicated that dicamba dissipated with a half-life range of 4.4 to 19.8 days. The DCSA was the major degradate in both studies. Both, dicamba and its degradate (DCSA) were found in soil segments deeper than 10 cm.

Aerobic soil metabolism is the main degradative process for dicamba. A single observed half-life for dicamba was six days; with formation of the intermediate non-persistent degradate DCSA. DCSA degraded at roughly the same rate as dicamba; the final metabolites were carbon dioxide and microbial biomass. Dicamba is stable to abiotic hydrolysis at all pH's and photodegrades slowly in water and on soil. Dicamba is more persistent under anaerobic soil:water systems in the laboratory, with a half-life of 141 days. The major degradate under anaerobic conditions was DCSA, which was persistent, comprising > 60% of the applied dose after 365 days of anaerobic incubation. No other anaerobic degradates were present at > 10% during the incubation. There are no acceptable data for the aerobic aquatic metabolism of dicamba; supplemental information indicates that dicamba degrades more rapidly in aquatic systems when sediment is present (Memo, Ibrahim Abdel-Saheb, D317705, 5/31/2005).

Dicamba is not expected to bioaccumulate in aquatic organisms because it is an anion at environmental pHs (pKa = 1.9).

### 5.1.3 Comparison of Metabolic Pathways

The metabolism of dicamba is qualitatively similar in all plants. Dicamba is metabolized in plants mainly by demethylation and hydroxylation. The main metabolites are 5-hydroxydicamba and DCSA. The metabolite 2,5-dichloro-3,6-dihydroxybenzoic acid (DCGA) has been recently identified in dicamba-tolerant plants. DCGA is formed by the hydroxylation of DCSA. In dicamba tolerant plants, the relative amounts of the metabolites DCSA, 5-OH dicamba and DCGA vary significantly when compared to the corresponding dicamba non-tolerant plants. Metabolism in ruminants was similar to poultry, the metabolism proceeds in a similar fashion to that seen in plants described above, however, an additional metabolite, 2-amino-3,6-

dichlorophenol has been identified in low amounts only in hen liver. In rat, dicamba is rapidly absorbed and excreted. The compound is not metabolized or accumulated by the tissues.

### 5.1.4 Residues of Concern Summary and Rationale

The risk assessment team for dicamba-tolerant cotton and soybean met in consultation with the co-chairs of the HED Residues of Concern Knowledgebase Sub-committee (ROCKS) on March 18, 2013 to discuss determining the residues of concern (ROC) for tolerance and risk assessment. The team concluded that parent dicamba, DCSA, and 5-OH dicamba were residues of concern in cotton for both tolerance expression and risk assessment, while they were the ROC in soybean for tolerance setting only. The ROC for soybean for risk assessment were parent dicamba, DCSA, DCGA and 5-OH dicamba (D410934, A. Kamel & P. Savoia, 06/03/2013).

Based on the results obtained from the metabolism and field trial studies, the residues present in both soybean and dicamba-tolerant soybean were comprised of dicamba, 5-hydroxydicamba, DCSA and DCGA. HED and PMRA evaluated both the exposure and hazard profiles for dicamba, 5-OH dicamba, DCSA and DCGA. Based on available toxicity studies and structural similarities, HED considers the parent and all three metabolites to be of comparable toxicity. The submitted data supported the existing tolerance expression for dicamba on soybean which includes parent dicamba, the DCSA metabolite and the 5-OH dicamba metabolite found in non-resistant varieties as the residues monitored in the tolerance expression. Since dicamba, 5-OH dicamba, and DCSA account for the majority of residues in tolerant and/or non-tolerant soybean, this tolerance expression provides sufficient residues to monitor for misuse for both tolerant and non-tolerant soybean; therefore the ROC for tolerance setting purposes is dicamba, 5-OH dicamba and DCSA. DCGA was not considered necessary for determining misuse; and thus was not added to the tolerance expression. The DCGA metabolite was included because it is present in appreciable concentrations up to 7.6 ppm (mean = 2.66 ppm) in feed items and in quantifiable amounts up to 0.14 ppm (mean = 0.032 ppm) in the seed in the registrant's submitted field trial data. In addition, amounts of DCGA found in soybean processed seed fractions were comparable to the amounts of DCSA.

The newly submitted data for dicamba-tolerant cotton supports including parent and the DCSA metabolite, along with the 5-OH dicamba metabolite found in non-resistant varieties as the residues of concern in cotton for tolerance expression and risk assessment. The rationale for this decision follows that residues present in both cotton and dicamba-tolerant cotton were comprised of dicamba, and its metabolites, 5-OH dicamba, DCSA, and DCGA. However, dicamba, 5-OH dicamba, and DCSA account for the majority of the residues in both tolerant and non-tolerant cotton and will provide sufficient residues with which to monitor for misuse for both tolerant and non-tolerant cotton; therefore, the ROC for tolerance setting purposes is dicamba, 5-OH dicamba, and DCSA.

For the purpose of risk assessment, HED considered both the exposure and hazard profiles for dicamba, 5-OH dicamba, DCSA, and DCGA and is including dicamba, 5-OH dicamba, and DCSA as the ROC for tolerant and non-tolerant cotton. While DCGA may be of comparable toxicity, it was present in the cotton metabolism studies at less than 10% of the total radioactive residue (TRR), and is only detected in livestock feed items, not in human food items. Further,

inclusion of this metabolite as a ROC in feed items would have no material impact on the livestock dietary burden since calculation of the reasonably balanced livestock diets are driven by other feed items with far higher residues. Therefore, HED is not including the DCGA metabolite as a ROC on cotton for risk assessment.

The residues of concern that are included for tolerance expression and risk assessment based on all the available data for dicamba are presented below in Table 5.1.4.

**Table 5.1.4. Dicamba Residues of Concern.**

| Matrix | Tolerance Expression | Residues for Risk Assessment |
|---|---|---|
| Barley, corn, grasses, oats, proso millet, sorghum, sugarcane, and wheat | Dicamba + 5-OH dicamba | Dicamba + 5-OH dicamba |
| Asparagus | Dicamba + DCSA[1] | Dicamba + DCSA |
| Cotton | Dicamba + 5-OH dicamba + DCSA | Dicamba + 5-OH dicamba + DCSA |
| Soybeans, and aspirated grain fractions (AGFs) | Dicamba + 5-OH dicamba + DCSA | Dicamba + 5-OH dicamba + DCSA + DCGA[2] |
| Livestock | Dicamba + DCSA | Dicamba + DCSA |
| Drinking Water | NA[3] | Dicamba + DCSA |

[1] DCSA also referred to as 3,6-dichloro-2-hydroxybenzoic acid or as 3,6-dichlorosalicylic acid.
[2] DCGA is also referred to as 2,5-dichloro-3,6- dihydroxybenzoic acid.
[3] NA – Not Applicable.

## 5.2 Food Residue Profile

The application of dicamba to crops primarily results in surface residues being found. For the proposed uses on dicamba-tolerant soybean and cotton, adequate crop field trial data were provided. These data are used to provide the basis for determining the recommended tolerances, as well as constructing the supporting dietary risk assessment.

The residue chemistry database for dicamba is adequate to support the proposed new uses on dicamba-tolerant soybeans and cotton. The nature of the residue is adequately understood based on prior metabolism studies made on wheat, grape, asparagus, sugarcane, cotton, and soybean, as well as on new ones provided for dicamba-tolerant soybean and cotton. Data on the metabolism of dicamba in dicamba-tolerant soybean and cotton demonstrate that dicamba is rapidly absorbed and translocated in the plants. The nature of the residue is adequately understood in livestock based on previous metabolism studies made on ruminants and poultry. The highest levels of dicamba residues in beef accumulated in kidney and liver tissues. The occurrence of quantifiable residues of dicamba or DCSA in poultry eggs and meat as a result of treating crops with poultry feed items at the maximum use patterns are not anticipated. There are adequate methods available for the enforcement of tolerances established on all plant and livestock commodities. Adequate storage stability data are available which demonstrate residues of dicamba are stable when stored frozen in dicamba-tolerant soybeans for up to 9.6 months, and dicamba-tolerant cotton for up to 6 months.

In the submitted field trials made on dicamba-tolerant soybeans, there were detectable levels of dicamba and its metabolites found in seed. Levels were found above the limits of detection at concentrations well below the previously established 10.0 ppm tolerance for non-resistant

soybean seed; therefore, the 10.0 ppm tolerance for soybean seed remains adequate. For the field trials provided on dicamba-tolerant cotton, detectable levels were found above the 0.2 ppm tolerance previously established for non-resistant cotton seed. Using the Organization for Economic Cooperation and Development (OECD) calculation procedures and inputting the total residues, a tolerance of 3.0 ppm is recommended for cotton seed.

Tolerances are recommended of 60 ppm on soybean forage, 100 ppm on soybean hay, and 70 ppm on cotton gin byproducts, which are livestock feed items. However, these tolerances will not increase livestock dietary burden; therefore, no new revised tolerances on livestock commodities are required.

For the registration of the new BAPMA salt formulation of dicamba, side-by-side field trials on representative crops were made to show product equivalency. Bridging studies provided for pasture grasses, wheat, field corn, and soybeans show that the average combined residues of dicamba are similar in the new BAPMA product with respect to the registered DGA salt formulation with all results falling well below established tolerance limits.

No new rotational crop data have since been submitted; therefore, the plant back restrictions noted in the 2005 RED are appropriately specified on the proposed product label for treating these dicamba-tolerant crops. Specifically, that a 120-day PBI is followed when dicamba is applied at a maximum seasonal rate of 0.75 lb ae/A or less. At seasonal application rates of 0.75-2.0 lb ae/A, only crops with established tolerances can be rotated for planting.

Processing study data were provided and residues of dicamba were found not to concentrate in the processed commodities of dicamba-tolerant cotton, but slightly concentrated in soybean hull (1.4 ×), flour (1.2 ×) and meal (1.3 ×) fractions. Based on the maximum residues found in soybean seeds and processed fractions using a 50% exaggerated application rate, the existing tolerances for soybean seed of 10 ppm and soybean hull at 30 ppm are adequate.

## 5.3 Water Residue Profile

Residues of dicamba and its DCSA degradate are known to be persistent in the environment and can reach drinking water supplies for human consumption. As a result, the Environmental Fate and Effects Division (EFED) provided drinking water exposure estimates for risk assessment (D404824, R. Baris, 03/28/2013). This assessment remains current since no new fate data have been submitted and it was derived with the latest models used by EFED for estimating pesticide residues in drinking water (personal communication, M. Corbin, 08/19/2015). For this determination, EFED conducted a Tier I PRZM GW drinking water assessment from groundwater sources for the proposed new uses. Residues of concern for drinking water for risk assessment purposes were the parent and its DCSA metabolite. Tables 5.3.1 – 5.3.4 provide the modeling estimates for drinking water summarized from surface water and ground water sources. For the purposes of this assessment, the highest (most conservative) PRZM-GW values were used for the acute (329 ppb parent + 0.041 ppb DCSA) and chronic (187 ppb parent + 0.041 ppb DCSA) assessments. The combined estimated drinking water residues (parent + DCSA) for peak concentration used in the acute assessment and chronic were 329 and 187 ug/L (ppb),

respectively. The model and its description are available at the EPA internet site: http://www.epa.gov/oppefed1/models/water/.

| Table 5.3.1. DICAMBA (parent only) Preliminary Cotton Runs for Dicamba (PCA corrected – 0.87) | | | | |
|---|---|---|---|---|
| Model | Use/Scenario | Acute (ug/L) | Chronic (ug/L) | 30-year average (ug/L) |
| SW (PRZM/EXAMS) | CAcotton_wirrgSTD.txt | 7.72 | 6.62 | 1.07 |
| | MScottonSTD.txt | ***53.37*** | ***44.5*** | ***6.52*** |
| | NCcottonSTD.txt | 32.14 | 27.32 | 4.24 |

| Table 5.3.2 DICAMBA (parent only) Preliminary Cotton Runs for Dicamba (PCA corrected – 0.87) | | | | |
|---|---|---|---|---|
| Groundwater | | Peak (ug/L) | Post breakthrough average (ug/L) | 30-year average (ug/L) |
| PRZM-GW (no pca applied) | GAcoastal | 41.9 | 28.2 | 24.9 |
| | DELMARVA | 192 | 121 | 117 |
| | FLCitrus | 238 | 161 | 155 |
| | FLPotato | 56.8 | 19.2 | 18.1 |
| | NCcoastal | 65.3 | 32.6 | 29.3 |
| | WIsands | ***329*** | ***187*** | ***158*** |
| SCIGROW | -- | 0.0015 | -- | -- |

Note: the highest estimates are in bold.

| Table 5.3.3 DCSA (PCA corrected – 0.87) | | | | |
|---|---|---|---|---|
| Model | Use/Scenario | Acute (ug/L) | Chronic (ug/L) | 30-year average (ug/L) |
| SW (PRZM/EXAMS) | MScottonSTD.txt | ***2.97*** | ***2.59*** | ***0.63*** |

| Table 5.3.4 DCSA (PCA corrected – 0.87) | | | | |
|---|---|---|---|---|
| Groundwater | | Peak (ug/L) | Post breakthrough average (ug/L) | 30-year average (ug/L) |
| PRZM-GW (no pca applied) | GAcoastal* | 4.47E-5 | 3.93E-5 | 2.38E-5 |
| | DELMARVA | 1.94E-4 | 1.65E-4 | 4.45E-5 |
| | FLCitrus | ***0.041*** | ***0.041*** | ***0.018*** |
| | FLPotato* | 5.71E-11 | 3.67E-11 | 3.114E-11 |
| | NCcoastal | 7.31E-5 | 3.64E-5 | 2.59E-5 |
| | WIsands* | 8.3E-4 | 7.66e-4 | 3.67E-4 |
| SCIGROW | -- | 0.0059 | -- | -- |

*100 year simulation

Note: the highest estimates are in bold.

In regard to the registration of the new Engenia herbicide, the BAPMA counter ion is known to have greater toxicity than the dicamba active ingredient. Because it is not possible to delineate exposure between the dicamba and BAPMA portion of the salt when this end-use product is applied, drinking water estimates must be adequately protective. To ensure the dicamba drinking water estimates are protective, EFED has examined drinking water exposures for dicamba versus the BAPMA counter ion (personal communication, W. Eckel, 07/15/2015). EFED used the Mississippi (MS) cotton scenario, a benchmark high-runoff scenario, to compare exposures from

applications of the BAPMA end-use product. This modeling found the 365-day average concentrations for dicamba-acid and BAPMA were comparable at 11 ppb and 11.8 ppb, respectively, for the Index Reservoir. The drinking water estimates provided are considered to be protective since the lowest adverse effect doses were selected for assessment.

## 5.4 Dietary Risk Assessment

### 5.4.1 Description of Residue Data Used in Dietary Assessment

Acute and chronic aggregate dietary food and drinking water exposure and risk assessments were conducted using the Dietary Exposure Evaluation Model software with the Food Commodity Intake Database (DEEM-FCID) Version 3.16. This software uses 2003-2008 food consumption data from the U.S. Department of Agriculture's (USDA's) National Health and Nutrition Examination Survey, What We Eat in America, (NHANES/WWEIA).

For this action there are several compounds to consider which include dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the dicamba BAPMA counter ion. The toxicological database is sufficient for assessing the toxicity of and characterizing the hazards of dicamba. Dicamba acid, the dicamba metabolites (DCSA, 5-OH dicamba, and DCGA), and the dicamba BAPMA counter ion are all considered because the lowest adverse effect doses were selected for dietary assessment.

The acute and chronic aggregate dietary risk assessments were conducted incorporating all current and proposed uses. Tolerance level residues for all commodities along with 100% CT were used in the acute dietary exposure assessments. A refined chronic dietary exposure assessment was performed which used average residues from field trial studies for crops, tolerance levels for livestock commodities, and relevant %CT data. Modeling estimates for ground water (PRZM-GW) were used to estimate residue concentrations in drinking water for both the acute and chronic assessments. The use of anticipated residues, empirical processing factors, and additional %CT data would refine further HED's exposure and risk estimates for dicamba.

### 5.4.2 Percent Crop Treated Used in Dietary Assessment

For the existing uses attributed to dicamba, BEAD provided a compilation of percent crop treated (%CT) data presented in Attachment 1 to aid in the refinement of the chronic dietary risk assessment ( D427534, J. Alsadek, 06/25/2015). The following average percent crop treated estimates were used in the chronic dietary risk assessment for the following crops that are currently registered for dicamba: asparagus: 5%; barley: 5%; corn: 10%; oats: 2.5%; sorghum: 15%; sugarcane: 20%; sweet corn: 1%; and wheat: 10%. One hundred percent crop treated was assumed for all other applicable crops (100 %CT).

### 5.4.3 Acute Dietary Risk Assessment

The acute analysis was an unrefined determination which used tolerance levels and 100 %CT for all existing and proposed uses. The dietary exposure analyses that were performed result in

acute dietary risk estimates that are below the Agency's level of concern for both food and water. For the U.S. population the exposure was 0.042760 mg/kg/day, which utilized 15% of the acute population adjusted dose (aPAD) at the 95th percentile. The highest exposure and risk estimates were for all infants. At the 95th percentile, the exposure for all infants was 0.088733 mg/kg/day, which utilized 31% of the aPAD.

### 5.4.4 Chronic Dietary Risk Assessment

The chronic analysis was a refined determination which used average residues based on field trial studies for crops, tolerance levels for livestock commodities, and relevant %CT data for several existing uses. The chronic risk estimates for dicamba are below the Agency's level of concern for the general U.S. population and all population subgroups. The most highly exposed population subgroup is children ages 1-2 with a risk estimate for dicamba for food and water of 42% of the cPAD.

### 5.4.5 Cancer Dietary Risk Assessment

Dicamba is classified as not likely to be carcinogenic to humans; therefore, a quantitative cancer dietary assessment was not performed.

### 5.4.6 Summary Table

**Table 5.4.6 Summary of Dietary (Food and Drinking Water) Exposure and Risk for Dicamba.**

| Population Subgroup | Acute Dietary[1] (95th Percentile) | | Chronic Dietary[2] | |
|---|---|---|---|---|
| | Dietary Exposure (mg/kg/day) | % aPAD | Dietary Exposure (mg/kg/day) | % cPAD |
| General U.S. Population | 0.042760 | 15 | 0.006319 | 16 |
| All Infants (< 1 year old) | **0.088733** | **31** | 0.014024 | 35 |
| Children 1-2 years old | 0.075295 | 26 | **0.016988** | **42** |
| Children 3-5 years old | 0.065788 | 23 | 0.011948 | 30 |
| Children 6-12 years old | 0.047142 | 16 | 0.007618 | 19 |
| Youth 13-19 years old | 0.032166 | 11 | 0.004936 | 12 |
| Adults 20-49 years old | 0.035172 | 12 | 0.005526 | 14 |
| Adults 50-99 years old | 0.029776 | 10 | 0.005340 | 13 |
| Females 13-49 years old | N/A[3] | N/A | 0.005465 | 14 |

[1] Acute dietary analysis derived from a 0.29 mg/kg/day aPAD for the general population.
[2] Chronic dietary analysis derived from a 0.04 mg/kg/day cPAD for the general population.
[3] N/A – not applicable, no endpoint was concluded for this population subgroup.
4 Highest exposures found for each assessment are noted in bold.

## 6.0 Residential (Non-Occupational) Exposure/Risk Characterization

There are no proposed residential uses at this time for either dicamba or the BAPMA salt; however, there are existing residential uses of dicamba that have been reassessed in this document to reflect updates to HED's 2012 Residential SOPs[1] along with policy changes for body weight assumptions. The revision of residential exposures will impact the human health aggregate risk assessment for dicamba. The proposed new BAPMA salt of dicamba does not impact the residential assessment as there are no proposed uses of dicamba BAPMA that would result in residential exposure; therefore, only the registered uses of dicamba have been reassessed in this document. Registered uses of dicamba include solid products or liquid products in concentrates or ready-to-use sprays for use as spot and broadcast treatments on turf.

## 6.1 Residential Handler Exposure

HED uses the term "handlers" to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct tasks related to applications and that exposures can vary depending on the specifics of each task. Residential handlers are addressed somewhat differently by HED as homeowners are assumed to complete all elements of an application without use of any protective equipment.

The quantitative exposure/risk assessment developed for residential handlers is based on the following lawn/turf application scenarios:

- Mix/Load/Apply Liquid with Hand-held Equipment
- Apply Ready-To-Use with Hand-held Equipment
- Load/Apply Granule with Hand-held Equipment

Residential Handler Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential handler risk assessments. Each assumption and factor is detailed below.

*Application Rate:*
The maximum application rate for residential products on turf is 1 lb ae/acre.

*Unit Exposures and Area Treated or Amount Handled:*
Unit exposure values and estimates for area treated or amount handled were taken from HED's 2012 Residential SOPs[1].

*Exposure Duration:*
Residential handler exposure is expected to be short-term in duration. Intermediate-term exposures are not likely because of the intermittent nature of applications by homeowners.

Residential Handler Non-Cancer Exposure and Risk Estimate Equations

[1] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

The algorithms used to estimate exposure and dose for residential handlers can be found in the 2012 Residential SOPs[2].

Combining Exposures/Risk Estimates:
There is no potential hazard *via* the dermal route for dicamba. Only inhalation risk estimates were quantitatively assessed.

Summary of Residential Handler Non-Cancer Exposure and Risk Estimates
The residential handler risk estimates are not of concern for dicamba (Inhalation MOEs > LOC of 30) for all scenarios.

**Table 6.1.1. Residential Handler Non-cancer Exposure and Risk Estimates for Dicamba Acid.**

| Exposure Scenario | Level of Concern | Inhalation Unit Exposure (mg/lb ai) | Maximum Application Rate[1] | Area Treated or Amount Handled Daily[2] | Inhalation | |
|---|---|---|---|---|---|---|
| | | | | | Dose (mg/kg/day)[5] | MOE[6] |
| Mixer/Loader/Applicator | | | | | | |
| Lawns/Turf, Liquid, Hose-end Sprayer | 30 | 0.022 | 1 lb ae/acre | 0.5 acres | 0.00014 | 510 |
| Lawns/Turf, Liquid, Sprinkler Can | | | 0.000023 lb ae/ft$^2$ | 1000 ft$^2$ | 0.0000063 | 11,000 |
| Lawns/Turf, Liquid, Manually-pressurized handwand | | 0.018 | 0.05 lb ae/gallon | 5 gallons | 0.000056 | 1,200 |
| Lawns/Turf, Liquid, Backpack | | 0.14 | | | 0.00044 | 160 |
| Lawns/Turf, RTU, Hose-end Sprayer | | 0.034 | 1 lb ae/acre | 0.5 acres | 0.00021 | 330 |
| Lawns/Turf, Granule, Push-type rotary spreader | | 0.0026 | 1 lb ae/acre | 0.5 acres | 0.000016 | 4,300 |
| Lawns/Turf, Granule, Belly grinder | | 0.039 | 0.000023 lb ae/ft$^2$ | 1200 ft$^2$ | 0.000013 | 5,200 |
| Lawns/Turf, Granule, Spoon | | 0.087 | | 100 ft$^2$ | 0.0000025 | 28,000 |
| Lawns/Turf, Granule, Cup/Shaker Can | | 0.013 | | | 0.00000037 | 190,000 |
| Lawns/Turf, Granule, Hand Dispersal | | 0.38 | | | 0.000011 | 6,400 |

Liquid = Liquid concentrate; RTU = Ready-to-use
1 Based on registered uses. Application rate is 1 lb ae/acre. 1 lb ae per acre with an assumed minimum of 20 gallons used per acre = 0.05 lb ae/gal; 1 lb ae/acre * 1 acre/43560 ft$^2$ = 0.0000344 lb ae/ft$^2$
2 Based on HED's 2012 Residential SOPs (http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide).
5 Inhalation Dose = Inhalation Unit Exposure (mg/lb ai) × Application Rate (lb ai/area or volume) × Area Treated or Amount Handled (area/day or volume/day) ÷ Body Weight (80 kg).
6 Inhalation MOE = Inhalation NOAEL (0.084 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## 6.2 Post-Application Exposure

There is the potential for post-application exposure for individuals exposed as a result of being in an environment that has been previously treated with dicamba. The quantitative exposure/risk assessment for residential post-application exposures is based on the following scenarios:

- Children (1 to < 2 years old) incidental oral exposure to treated turf.

[2] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

- Children (1 to < 2 years old) episodic granular ingestion exposure.

Assessment of post-application exposure to liquid formulations is protective of exposure to solid formulations, except for the episodic granular ingestion scenario which was quantitatively assessed.

The lifestages selected for each post-application scenario are based on an analysis provided as an Appendix in the 2012 Residential SOPs[3]. These lifestages are not the only lifestages that could be potentially exposed for these post-application scenarios; however, the assessment of these lifestages is health protective for the exposures and risk estimates for any other potentially exposed lifestages.

Residential Post-application Exposure Data and Assumptions
A series of assumptions and exposure factors served as the basis for completing the residential post-application risk assessment. Each assumption and factor is detailed in the 2012 Residential SOPs.

Turf Transferable Residue Data
There are chemical-specific turf transferable residue (TTR) data available for dicamba. Based on a review of all available data, TTR residues from MRID 44959001 were used to assess post-application exposure since the study was conducted at the maximum application rate being assessed, and predicted residues were consistent in three different site locations. Therefore, HED has used the predicted residue value of 0.15 $\mu g/cm^2$ from MRID 44959001 for risk assessment purposes.

Residential Post-application Non-Cancer Exposure and Risk Equations
The algorithms used to estimate residential post-application exposure and dose can be found in the 2012 Residential SOPs.

Combining Exposure and Risk Estimates
There is no potential hazard *via* the dermal route for dicamba. Only incidental oral risk estimates were quantitatively assessed. The incidental oral scenarios (i.e., hand-to-mouth and object-to-mouth) should be considered inter-related and it is likely that they occur interspersed amongst each other across time, therefore, these scenarios are not combined. The granular ingestion scenario is not combined as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning. Therefore, no post-application exposure scenarios were combined for children 1 < 2 years old.

Summary of Residential Post-application Non-Cancer Exposure and Risk Estimates
The residential post-application risk estimates are not of concern for dicamba (MOEs are greater than the level of concern of 100) for all incidental oral scenarios. All scenarios are short-term exposures, except episodic granular ingestion which is an acute scenario. Incidental soil

[3] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/standard-operating-procedures-residential-pesticide

ingestion scenario is short-term exposure only as the soil half-life for dicamba is 18 days (EFED memo, I. Maher, D378447, 11/22/10).

**Table 6.2.1. Residential Post-application Non-cancer Exposure and Risk Estimates for Dicamba.**

| Lifestage | Post-application Exposure Scenario | | Application Rate[1] | TTR ($ug/cm^2$)[2] | Dose (mg/kg/day) | MOE (LOC = 100)[3] |
|---|---|---|---|---|---|---|
| | Use Site | Route of Exposure | | | | |
| 1 to < 2 years old | Turf - liquid | Hand-to-Mouth | 1 lb ae/acre | 0.15 | 0.02055 | 6,600 |
| | | Object-to-Mouth | | | 0.00062 | 220,000 |
| | | Soil Ingestion | | | 0.000034 | 4,000,000 |
| | Turf- Granular | Episodic Granular Ingestion | 1% ai | | 0.09 | 320[A] |

1 Based on registered uses (reference: 2005 RED).
2 TTR based on MRID 44959001.
3 MOE = Incidental oral POD (136 mg/kg/day) ÷ Dose (mg/kg/day) for hand-to-mouth, object-to-mouth, and soil ingestion scenarios. LOC = 100.
A Ingestion of granules is considered episodic in nature; MOE was calculated using the acute dietary POD (29 mg/kg/day) and LOC (100).

## 6.3 Residential Risk Estimates for Use in Aggregate Assessment

Table 6.3.1 reflects the residential risk estimates that are recommended for use in the aggregate assessment for dicamba. Inhalation exposures are not included in the aggregate assessment since effects from the inhalation route are not systemic/cannot be aggregated. Post-application episodic granular ingestion following applications to lawns and turf are not included in the aggregate assessment as this exposure would not occur as a result of routine behavior and is considered an episodic event related to poisoning. There is no recommended residential exposure for use in the adult aggregate assessment since there is no hazard via the dermal route of exposure and inhalation exposures are not included in the aggregate assessment, as described above. Therefore, the only residential exposures recommended for the dicamba aggregate assessment are the following:

- The recommended residential exposure for use in the children (1 to <2 years old) aggregate assessment reflects hand-to-mouth exposures from post-application turf scenario (i.e., post-application exposure to treated turf).

**Table 6.3.1. Recommendations for the Residential Exposures for the Dicamba Aggregate Assessment.**

| Lifestage | Exposure Scenario | Dose (mg/kg/day)[1] | | | | MOE (LOC = 100)[2] | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Dermal | Inhalation | Incidental Oral | Total | Dermal | Inhalation | Incidental Oral | Total |
| Child | Hand-to-Mouth Post-application Exposure – Treated Turf | N/A | N/A | 0.02055 | **0.02055** | N/A | N/A | 6,600 | **6,600** |

1 Dose = the highest dose for each applicable lifestage of all residential scenarios assessed. Total = dermal + inhalation + incidental oral (where applicable).
2 MOE = the MOEs associated with the highest residential doses. Total = 1 ÷ (1/Dermal MOE) + (1/Inhalation MOE) + (1/Incidental Oral MOE), where applicable.

## 6.4 Residential Bystander Post-application Inhalation Exposure

The potential exposure to bystanders from vapor phase dicamba and BAPMA salt residues emitted from treated fields has been evaluated for the proposed uses of dicamba on dicamba-tolerant corn and soybean, and for the proposed uses of BAPMA on various agricultural crops. Bystander exposure to dicamba and BAPMA emitted from treated fields depends on two main factors: 1) the rate at which these chemicals volatilize from a treated field (described as the off-gassing, emission or flux), and 2) how those vapors are dispersed in the air over and around the treated field. Volatilization can occur during the application process or thereafter. It can result from aerosols evaporating during application, while deposited sprays are still drying (possibly via co-distillation), or after as dried deposited residues volatilize.

This assessment employs approaches EPA has used previously to assess inhalation exposures to fumigant pesticides[4] and is also consistent with the recommendations of the December 2009 Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP)[5] meeting on the scientific issues associated with field volatilization of conversional (semi-volatile) pesticides.

### 6.4.1 Flux Data

A submitted flux study[6] was reviewed by the Environmental Fate and Effects Division (EFED), which estimated the flux of dicamba vapors after spray application of the DGA salt formulation. The dicamba DGA salt formulation was used alone without any tank adjuvants, and the test surface was zoysiagrass. The trial was performed in August 2012 near Columbia, IL, and experienced minimum and maximum temperatures of 21.1°C and 26.2°C, respectively.

A circle in the zoysiagrass with a diameter of 40 m (~131 ft) was sprayed with a tank mix of 32 oz/A (1.0 lb a.e./A) Clarity® (EPA Reg. # 7969-137). Herbicide treatments were applied using a nitrogen pressurized backpack sprayer calibrated to deliver 10 gallons per acre (GPA) at 50 PSI using TeeJet® TTI 110015 spray tips. Application of the test substance was made approximately perpendicular to the prevailing wind direction. In the test plot, three air samplers and an anemometer were placed in the treatment area after post-application drift was allowed to settle (typically 2-5 minutes). Data were collected for 0-6 hours after application.

The field test method employed was the Theoretical Profile Shape (TPS) method which requires circular spray plots of a certain diameter, with air sampling and wind velocity measurements acquired at the center of the circle at a certain, single height determined by the circle size and the surface roughness. A short description of the TPS method and calculations is provided in an Appendix of the study report.

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[4] U.S. EPA 2004d. FIFRA Science Advisory Panel Meeting Minutes - Fumigant Bystander Exposure Model Review: Probabilistic Exposure and Risk Model for Fumigants (PERFUM) Using Iodomethane as a Case Study. Available at http://www.epa.gov/scipoly/sap/meetings/2004/august1/august2425minutes.pdf

[5] U.S. EPA 2009. FIFRA Science Advisory Panel Meeting Minutes - Scientific Issues Associated with Field Volatilization of Conventional Pesticides. Available at http://www.epa.gov/scipoly/sap/meetings/2009/december/120309meetingminutes.pdf

[6] Memo, D411382, W. Eckel. MRID 49022501. Sall, E.; Smith, H.; Findley, D.; et al. (2013) Measurement of the Volatile Flux of Dicamba under Field Conditions using the Theoretical Profile Shape Method. Project Number: RPN/2012/0662, MSL0024798. Unpublished study prepared by Monsanto Company. 52p.

The estimated 6 hr average flux from the Clarity® application on zoysiagrass was 0.4 (+/- 0.1) ng/m$^2$/sec, representing 0.008% of the application rate. Quantitative analysis using the estimated flux rate derived from this study is described below.

While the flux data are specific to the DGA salt of dicamba, it is considered protective for the BAPMA salt form of dicamba as well. BAPMA is considered less volatile than the DGA salt and, therefore, would be expected to result in lower air concentrations as a result of flux from a treated field. Based on modeling data using EPISuite and information provided in a BASF patent[7], the volatility of the BAPMA salt is lower than that of the DGA salt. EPISuite estimated the vapor pressure of the DGA salt as 1.48E-11 mmHg at 25°C, and for BAPMA as 1.10E-21 mmHg at 25°C. The BASF patent provides a relative ranking of the volatility of the various forms of dicamba (compared to the acid at 100%), with the BAPMA salt being 0.5% of the volatility of the dicamba acid and the DGA salt being 5.4% of the dicamba acid. Therefore, HED believes that the volatilization assessment conducted using the flux data for the DGA salt is protective of the BAPMA salt.

### 6.4.2 Volatilization Modeling and Risk Assessment

Exposure modeling for a single day was completed using Probabilistic Exposure and Risk model for FUMigants (PERFUM). There are a variety of factors that potentially affect the emission rates of dicamba and subsequent offsite transport including: field condition (bare soil, growing or mature crop canopy), field parameters (soil type, moisture, etc.), formulation type, meteorological conditions, and application scenario (rate, method). The flux estimate from the study (0.0004 ug/m$^2$/s), a single 40A field, and the Bradenton, FL meteorological data were used with PERFUM to estimate risk based on the dicamba field volatility study summarized in Section 6.4.1.

The short-term residential inhalation endpoints for dicamba and BAPMA were used in the volatilization assessment (dicamba acid: 530 ug/m$^3$ and LOC of 30; BAPMA salt: 50 ug/m$^3$; LOC = 300). This is considered a conservative assumption to compare the day 1 volatilization exposure to a short-term HEC. Furthermore, a 6-hour exposure averaging period was used in the model; it is a conservative assumption to compare the 6 hour average exposure from the model to the HEC calculated for 24 hours of exposure especially since the 6 hour exposure period used as the basis for the comparison represents the peak emissions period after application.

All of the files associated with the use of PERFUM in this assessment can be provided upon request. These files could be used to examine the detailed input and output files for each permutation of the model completed for this analysis.

### 6.4.3 Volatilization Risk Estimates

The field volatility study suggests that volatilization of dicamba from treated crops does occur, and it has been assumed that is true also for the BAPMA salt, which could result in bystander

[7] Low volatile amine salts of anionic pesticides. USPTO Application: #20150210723. http://images3.freshpatents.com/pdf/US20150210723A1.pdf

exposure. Results of PERFUM modeling, however, indicate that airborne concentrations, even at the edge of the treated fields, are not of concern. The maximum proposed application rate of 1 lb ae/A was assessed. There were no whole field and maximum field buffers estimated using PERFUM (i.e., risks were acceptable at all percentiles of exposure at the edge of a treated field).

## 6.5 Non-Occupational Spray Drift Exposure and Risk Estimates

Off-target movement of pesticides can occur via many types of pathways and it is governed by a variety of factors. Sprays that are released and do not deposit in the application area end up off-target and can lead to exposures to those it may directly contact. They can also deposit on surfaces where contact with residues can eventually lead to indirect exposures (*e.g.*, children playing on lawns where residues have deposited next to treated fields). The potential risk estimates from these residues can be calculated using drift modeling coupled with methods employed for residential risk assessments for turf products.

The approach to be used for quantitatively incorporating spray drift into risk assessment is based on a premise of compliant applications which, by definition, should not result in direct exposures to individuals because of existing label language and other regulatory requirements intended to prevent them.[8] Direct exposures would include inhalation of the spray plume or being sprayed directly. Rather, the exposures addressed here are thought to occur indirectly through contact with impacted areas, such as residential lawns, when compliant applications are conducted. Given this premise, exposures for children (1 to 2 years old) and adults who have contact with turf where residues are assumed to have deposited via spray drift thus resulting in an indirect exposure are the focus of this analysis analogous to how exposures to turf products are considered in risk assessment.

*Dicamba:* Several dicamba products have existing labels for use on turf, thus it was considered whether the risk assessment for that use may be considered protective of any type of exposure that would be associated with spray drift. It should be noted that the registered residential uses on turf result in exposure greater than potential exposure from spray drift; therefore, no new residential assessment needs to be completed. If the maximum application rate on crops adjusted by the amount of drift expected is less than or equal to existing turf application rates, the existing turf assessment is considered protective of spray drift exposure. The proposed maximum single application rate of dicamba is 1 lb ae/A. The highest degree of spray drift noted for any application method immediately adjacent to a treated field (Tier 1 output from the aerial application using fine to medium spray quality) results in a deposition fraction of 0.26 of the application rate. A quantitative spray drift assessment for dicamba is not required because the maximum application rate to a crop/target site multiplied by the adjustment factor for drift of 0.26 is less than the maximum direct spray residential turf application rate 1 lb ae/A[9] for any dicamba products. The turf post-application MOEs have been previously assessed and are based on the revised SOPs for Residential Exposure Assessment (i.e., see above in Section 6.2).

[8] This approach is consistent with the requirements of the EPA's Worker Protection Standard which, when included on all labels, precludes direct exposure pathways.

[9] 1 lb ae/A x 0.26 ≤ 1 lb ae/A

*BAPMA salt:* In order to evaluate the drift potential and associated risks for the BAPMA salt, an approach based on drift modeling coupled with techniques used to evaluate residential uses of pesticides was utilized. Essentially, a residential turf assessment based on exposure to deposited residues has been completed to address drift from the agricultural applications of the BAPMA salt. In the spray drift scenario, the deposited residue value was determined based on the amount of spray drift that may occur at varying distances from the edge of the treated field using the AgDrift (v2.1.1) model and the *Residential Exposure Assessment Standard Operating Procedures Addenda 1: Consideration of Spray Drift Policy*. Once the deposited residue values were determined, the remainder of the spray drift assessment was based on the algorithms and input values specified in the recently revised (2012) *Standard Operating Procedures For Residential Risk Assessment (SOPs)*.

A screening approach was developed based on the use of the AgDrift model in situations where specific label guidance that defines application parameters is not available.[10] AgDrift is appropriate for use only when applications are made by aircraft, airblast orchard sprayers, and groundboom sprayers. When AgDrift was developed, a series of screening values (i.e., the Tier 1 option) were incorporated into the model and represent each equipment type and use under varied conditions. The screening options specifically recommended in this methodology were selected because they are plausible and represent a reasonable upper bound level of drift for common application methods in agriculture. These screening options are consistent with how spray drift is considered in a number of ecological risk assessments and in the process used to develop drinking water concentrations used for risk assessment. In all cases, each scenario is to be evaluated unless it is not plausible based on the anticipated use pattern (e.g., herbicides are not typically applied to tree canopies) or specific label prohibitions (e.g., aerial applications are not allowed).

The spray drift risk estimates are based on an estimated deposited residue concentration as a result of the screening level agricultural application scenarios. BAPMA salt is proposed for use on numerous agricultural crops and can be applied via aerial and ground boom equipment. The recommended drift scenario screening level options are listed below:

- **Groundboom applications** are based on the AgDrift option for high boom height and using very fine to fine spray type using the 90$^{th}$ percentile results.
- **Aerial applications** are based on the use of AgDrift Tier 1 aerial option for a fine to medium spray type and a series of other parameters which will be described in more detail below (e.g., wind vector assumed to be 10 mph in a downwind direction for entire application/drift event).

Only incidental oral risk estimates were estimated since there is not dermal hazard for the BAPMA salt. The total applicable LOC is 100 so MOEs < 100 would be of concern. Children's (1<2 year old) incidental oral risk estimates from indirect exposure to dicamba BAPMA salt related to spray drift result in no risk estimates of concern at the field edge for groundboom and aerial applications (i.e., all MOEs ≥ 35,000).

[10]http://www.agdrift.com/

| Table 6.5.1. Non-occupational Risk Estimates Resulting from Spray Drift for BAPMA Salt. | | | | |
|---|---|---|---|---|
| Crop/Rate Group | Spray Type/ Nozzle Configuration | Application Rate (lb ai/A) | Estimated $TTR_t$ (ug/cm$^2$)[a] | HtM MOE at Field Edge (LOC = 100) |
| Aerial | Fine to Medium | 1 | 0.11115 | 35,000 |
| Ground boom | High Boom Very fine to Fine | | | 48,000 |

a. TTR = Application Rate × F × (1-D)$^t$ × 4.54E8 µg/lb × 2.47E-8 acre/cm$^2$.

## 7.0 Aggregate Exposure/Risk Characterization

In accordance with the FQPA, HED must consider and aggregate (add) pesticide exposures and risks from three major sources: food, drinking water, and residential exposures. In an aggregate assessment, exposures from relevant sources are added together and compared to quantitative estimates of hazard, or the risks themselves can be aggregated. When aggregating exposures and risks from various sources, HED considers both the route and duration of exposure. Since residential exposure is expected, aggregate exposure consists of exposure from residential, food and drinking water sources.

Acute and chronic aggregate risks include only dietary exposure from food and drinking water sources. Since there are residential uses, short-term aggregate risks were assessed which include contributions from food, drinking water, and residential exposure. Intermediate-term aggregate risks were not considered as residential exposure is not expected to occur for more than 30 days. Cancer aggregate risk was not quantified since dicamba is not a carcinogen. A common toxicological endpoint (decreased pup growth) of concern was not identified for short-, intermediate- and long-term durations via the oral, dermal (oral equivalent) and inhalation (oral equivalent) routes. Therefore, the aggregate exposure risk assessment should include exposure across the oral routes as appropriate for the populations of concern (i.e. food and water for adults and food, water and incidental oral for children).

### 7.1 Acute Aggregate Risk

It is HED policy not to aggregate non-distributional acute residential exposures with acute dietary exposures, since it is unlikely that these types of exposures would occur in the same day. Thus, the acute dietary (food and drinking water) assessment in Section 5.4 represents acute aggregate risk. The acute dietary exposure assessment was conducted using tolerance-level residues, DEEM default processing factors and 100% crop-treated information for all registered and proposed use sites. Drinking water values were incorporated directly into the assessment.

The most highly exposed population subgroup is all infants (<1 year old; 31% of the aPAD). The acute and chronic dietary exposure estimates are not of concern for the general U.S. population or any population subgroup.

### 7.2 Short-Term Aggregate Risk

The short term aggregate assessment is comprised of exposure from food, drinking water and residential activities (handler and post-application). Average food and water exposure estimates were used in the assessment. The residential scenario that resulted in the highest exposures for children was the post-application exposure on turf.

The results of the short-term aggregate assessments for children is presented in Table 7.2. The MOE is greater than 100 for children scenario, thus are not of concern to HED. For adults, there is no short-term aggregate assessment, since there was no dermal hazard identified in the route-specific dermal studies and the inhalation effects were not systemic. As stated in the previous section, these results are likely to be over-estimates and the actual exposures are likely to be much lower.

**Table 7.2. Short-Term Term Aggregate Risk Calculations**

| Population | Short-Term Scenario | | | | | | |
|---|---|---|---|---|---|---|---|
| | NOAEL mg/kg/day | LOC[1] | Max Allowable Exposure[2] mg/kg/day | Average Food and Water Exposure mg/kg/day | Residential Exposure mg/kg/day[3] | Total Exposure mg/kg/day[4] | Aggregate MOE (food, water, and residential)[5] |
| Child (1-2 years) | 136 | 100 | 0.45 | 0.016988 | 0.02055 | 0.037538 | 3600 |

[1] LOC is 100 (10X for inter-species and 10X for intra-species)
[2] Maximum Allowable Exposure (mg/kg/day) = NOAEL/LOC
[3] Residential Exposure = [Oral exposure + Dermal exposure + Inhalation Exposure]. See Table 5.4.1
[4] Total Exposure = (Avg Food & Water Exposure + Residential Exposure)
[5] Aggregate MOE = [NOAEL / (Avg Food & Water Exposure + Residential Exposure)]

## 7.3 Intermediate-Term Aggregate Risk

Not Applicable

## 7.4 Chronic Aggregate Risk

Since the residential uses of dicamba are not expected to occur over the long-term (or chronic) duration, chronic aggregate risk is comprised of dietary exposure only, from food and drinking water sources. The chronic dietary assessment in Section 5.4 represents chronic aggregate risk. The chronic dietary exposure assessment was conducted using average field trial data, DEEM default processing factors and available %CT information for all registered and proposed use sites. Drinking water values were incorporated directly into the assessment.

The most highly exposed population sub-group is children 1-2 years old (42% of the cPAD). Chronic aggregate risk is not of concern for any population.

## 7.5 Cancer Aggregate Risk

Dicamba is classified as not likely to be carcinogenic to humans, thus a quantitative aggregate cancer risk is not applicable and not assessed. This conclusion was based on the lack of findings in cancer studies in rats and mice which were tested at adequate dose levels to assess the

carcinogenicity of dicamba (TXR No. 0053647). Additionally, the DCSA metabolite had a lack of cancer findings in its rat carcinogenicity study.

## 8.0 Cumulative Exposure/Risk Characterization

Unlike other pesticides for which EPA has followed a cumulative risk approach based on a common mechanism of toxicity, EPA has not made a common mechanism of toxicity finding for dicamba and any other substance, and dicamba does not appear to produce a toxic metabolite produced by other substances. For the purposes of this tolerance action, therefore, EPA has assumed that dicamba does not have a common mechanism of toxicity with other substances. For information regarding EPA's efforts to determine which chemicals have a common mechanism of toxicity and to evaluate the cumulative effects of such chemicals, see the policy statements released by EPA's Office of Pesticide Programs concerning common mechanism determinations and procedures for cumulating effects from substances found to have a common mechanism on EPA's website at http://www.epa.gov/pesticides/cumulative/.

## 9.0 Occupational Exposure/Risk Characterization

### 9.1 Short-/Intermediate-Term/ Handler Risk

HED uses the term handlers to describe those individuals who are involved in the pesticide application process. HED believes that there are distinct job functions or tasks related to applications and exposures can vary depending on the specifics of each task. Job requirements (amount of chemical used in each application), the kinds of equipment used, the target being treated, and the level of protection used by a handler can cause exposure levels to differ in a manner specific to each application event.

Based on the anticipated use patterns and current labeling, types of equipment and techniques that can potentially be used, occupational handler exposure is expected from the proposed uses. The quantitative exposure/risk assessment developed for occupational handlers for the dicamba DGA salt uses is based on the following scenarios:

- Mixing/loading liquid in support of ground boom application to high-acreage crops (cotton and soybean)
- Applying spray by ground boom equipment to high acreage crops (cotton and soybean)

The quantitative exposure/risk assessment developed for occupational handlers for the dicamba BAPMA salt uses is based on the following scenarios:

- Mixing/loading liquid in support of aerial application to sod, typical field crops (asparagus), and high-acreage crops (corn, soybean, cotton, sugarcane)
- Mixing/loading liquid in support of ground boom application to sod, typical field crops (asparagus), and high-acreage crops (corn, soybean, cotton, sugarcane)
- Applying spray by aerial equipment to sod, typical field crops, and high-acreage crops
- Applying spray by ground boom equipment to sod, typical field crops, and high-acreage crops

- Flagging in support of aerial application to sod, typical field crops, and high-acreage crops

Occupational Handler Exposure Data and Assumptions

A series of assumptions and exposure factors served as the basis for completing the occupational handler risk assessments. Each assumption and factor is detailed below on an individual basis.

*Application Rate*:
See Section 3 for a summary of use directions and application rates.

*Unit Exposures:* It is the policy of HED to use the best available data to assess handler exposure. Sources of generic handler data, used as surrogate data in the absence of chemical-specific data, include PHED 1.1, the AHETF database, the Outdoor Residential Exposure Task Force (ORETF) database, or other registrant-submitted occupational exposure studies. Some of these data are proprietary (e.g., AHETF data), and subject to the data protection provisions of FIFRA. The standard values recommended for use in predicting handler exposure that are used in this assessment, known as "unit exposures", are outlined in the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table[11]", which, along with additional information on HED policy on use of surrogate data, including descriptions of the various sources, can be found at the Agency website[12].

*Area Treated or Amount Handled:*
Based on ExpoSAC Policy 9.1:

- The area treated for ground boom application to sod and typical field crops is 80 acres per day and to high acreage crops is 200 acres per day.
- The area treated for aerial application to sod and typical field crops is 350 acres per day and to high acreage crops is 1200 acres per day.

*Exposure Duration:*
HED classifies exposures from 1 to 30 days as short-term and exposures 30 days to six months as intermediate-term. Exposure duration is determined by many factors, including the exposed population, the use site, the pest pressure triggering the use of the pesticide, and the cultural practices surrounding that use site. For most agricultural uses, it is reasonable to believe that occupational handlers will not apply the same chemical every day for more than a one-month time frame; however, there may be a large agribusiness and/or commercial applicators who may apply a product over a period of weeks (e.g., completing multiple applications for multiple clients within a region).

For dicamba, based on the proposed use, short- and intermediate-term exposures are expected as the product can have multiple applications to the crop throughout the season and applicators may apply the product to multiple farms throughout the growing season.

[11] Available http://www2.epa.gov/sites/production/files/2015-09/documents/handler-exposure-table-2015.pdf
[12] Available: http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data

*Mitigation/Personal Protective Equipment:* Estimates of inhalation exposure were calculated for various levels of personal protective equipment (PPE) or engineering controls. Results are presented for "baseline," defined as no respirator, as well as with various levels of respiratory protection. The dicamba product labels currently do not require respiratory protection.

Occupational Handler Non-Cancer Exposure and Risk Estimate Equations

The algorithms used to estimate non-cancer exposure and dose for occupational handlers can be found in Appendix A of the ORE document.

Combining Exposures/Risk Estimates:

There is no potential hazard *via* the dermal route for dicamba. Only inhalation risk estimates were quantitatively assessed.

Summary of Occupational Handler Non-Cancer Exposure and Risk Estimates

*DGA salt of dicamba*: The occupational handler risk estimates are not of concern for dicamba acid (inhalation MOEs > LOC of 30) for all scenarios with label required PPE (i.e., no respiratory protection). See Table 9.1.1 below.

**Table 9.1.1. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba acid (DGA salt).**

| Exposure Scenario | Crop or Target | Inhalation Unit Exposure (µg/lb ai)[1] | Maximum Application Rate[2] | Area Treated or Amount Handled Daily[3] | Inhalation | |
|---|---|---|---|---|---|---|
| | | Baseline Mitigation Level (No Respiratory Protection) | | | Dose (mg/kg/day)[4] | MOE (LOC = 30)[5] |
| **Mixer/Loader** | | | | | | |
| Mixing/Loading Liquid in Support of Ground boom Application | High Acreage Crops | 0.219 | 1 lb ae/acre | 200 acres | 0.000548 | 380 |
| **Applicator** | | | | | | |
| Applying Spray by Ground boom Application | High Acreage Crops | 0.34 | 1 lb ae/acre | 200 acres | 0.00085 | 250 |

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2016).
2 Based on proposed label (Reg. No. 524-582).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (kg).
5 Inhalation MOE = Inhalation POD (0.21 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

*BAPMA salt of dicamba*: Most occupational handler risk estimates are of concern for dicamba BAPMA salt (inhalation MOEs < LOC of 300) based on label-required PPE (i.e., no respiratory protection). See Table 9.1.2 for a summary of handler risk estimates below. A summary of handler risk estimates with additional inhalation PPE/ engineering controls to mitigate risks is provided in Table 9.1.3; some handler risk estimates are still of concern with the maximum PPE/ engineering controls. Note that HED has no data to assess exposures to pilots using open cockpits. The only data available is for exposure to pilots in enclosed cockpits (i.e., engineering controls). Therefore, in both tables, aerial applicator risk estimates are shown representing the use of engineering controls.

**Table 9.1.2. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba BAPMA (Label Required PPE = No Respirator).**

| Exposure Scenario | Crop or Target | Inhalation Unit Exposure (µg/lb ai)[1] Baseline Mitigation Level (No Respiratory Protection Unless Otherwise Specified) | Maximum Application Rate[2] | Area Treated or Amount Handled Daily[3] | Inhalation Dose (mg/kg/day)[4] | Inhalation MOE (LOC = 300)[5] |
|---|---|---|---|---|---|---|
| **Mixer/Loader** | | | | | | |
| Mixing/Loading Liquid in Support of Aerial Application | Sod | 0.219 | 0.5 lb ae/A | 350 acres | 0.000479 | **42** |
| | Typical Field Crops | | 1 lb ae/A | 350 acres | 0.000959 | **21** |
| | High Acreage Field Crops | | | 1200 acres | 0.00329 | **6.1** |
| Mixing/Loading Liquid in Support of Ground boom Application | Sod | | 0.5 lb ae/A | 80 acres | 0.00011 | **180** |
| | Typical Field Crops | | 1 lb ae/A | 80 acres | 0.000219 | **91** |
| | High Acreage Crops | | | 200 acres | 0.000548 | **36** |
| **Applicator** | | | | | | |
| Applying Spray via Aerial Application | Sod | Engineering Control: 0.0049 | 0.5 lb ae/A | 350 acres | 0.0000107 | 1,900 |
| | Typical Field Crops | | 1 lb ae/A | 350 acres | 0.0000215 | 930 |
| | High Acreage Field Crops | | | 1200 acres | 0.0000735 | **270** |
| Applying Spray by Ground boom Application | Sod | 0.34 | 0.5 lb ae/A | 80 acres | 0.00017 | **120** |
| | Typical Field Crops | | 1 lb ae/A | 80 acres | 0.00034 | **59** |
| | High Acreage Crops | | | 200 acres | 0.00085 | **24** |
| **Flagger** | | | | | | |
| Flagging in support of Aerial Application | Sod | 0.35 | 0.5 lb ae/A | 350 acres | 0.000766 | **26** |
| | Typical Field Crops | | 1 lb ae/A | | 0.00154 | **13** |
| | High Acreage Field Crops | | | | 0.00154 | **13** |

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2016).
2 Based on proposed label (7969-GUL).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation Dose = Inhalation Unit Exposure (µg/lb ai) × Conversion Factor (0.001 mg/µg) × Application Rate (lb ai/acre or gal) × Area Treated or Amount Handled (A or gal/day) ÷ BW (kg).
5 Inhalation MOE = Inhalation POD (0.02 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

**Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba BAPMA (with additional respiratory protection).**

| Exposure Scenario | Crop or Target | Inhalation Unit Exposure (µg/lb ai)[1] Mitigation Level | Maximum Application Rate[2] | Area Treated or Amount Handled Daily[3] | Inhalation MOE (LOC = 300)[4] PF5 | PF10 | Eng. Control |
|---|---|---|---|---|---|---|---|
| **Mixer/Loader** | | | | | | | |
| Mixing/Loading Liquid | Sod | PF5: 0.0438 | 0.5 lb ae/A | 350 acres | **210** | 420 | **110** |

**Table 9.1.3. Occupational Handler Non-Cancer Exposure and Risk Estimates for Dicamba BAPMA (with additional respiratory protection).**

| Exposure Scenario | Crop or Target | Inhalation Unit Exposure (µg/lb ai)[1] | Maximum Application Rate[2] | Area Treated or Amount Handled Daily[3] | Inhalation MOE (LOC = 300)[4] | | |
|---|---|---|---|---|---|---|---|
| | | Mitigation Level | | | PF5 | PF10 | Eng. Control |
| in Support of Aerial Application | Typical Field Crops | PF10: 0.0219 EC: 0.083 | 1 lb ai/A | 350 acres | **100** | **210** | **55** |
| | High Acreage Field Crops | | | 1200 acres | **30** | **61** | **16** |
| Mixing/Loading Liquid in Support of Ground boom Application | Sod | | 0.5 lb ae/A | 80 acres | 910 | 1.800 | 480 |
| | Typical Field Crops | | 1 lb ae/A | 80 acres | 460 | 910 | **240** |
| | High Acreage Crops | | | 200 acres | **180** | 360 | **96** |
| **Applicator** | | | | | | | |
| Applying Spray via Aerial Application | Sod | EC: 0.0049 | 0.5 lb ae/A | 350 acres | NA | NA | 1,900 |
| | Typical Field Crops | | 1 lb ae/A | 350 acres | NA | NA | 930 |
| | High Acreage Field Crops | | | 1200 acres | NA | NA | **270** |
| Applying Spray by Ground boom Application | Sod | PF5: 0.068 PF10: 0.034 EC: 0.043 | 0.5 lb ae/A | 80 acres | 590 | 1,200 | 930 |
| | Typical Field Crops | | 1 lb ae/A | 80 acres | **290** | 590 | 470 |
| | High Acreage Crops | | | 200 acres | **120** | **240** | 190 |
| **Flagger** | | | | | | | |
| Flagging in support of Aerial Application | Sod | PF5: 0.07 PF10: 0.035 | 0.5 lb ae/A | 350 acres | **130** | **260** | NA |
| | Typical Field Crops | | 1 lb ae/A | | **65** | **130** | NA |
| | High Acreage Field Crops | | | | **65** | **130** | NA |

1 Based on the "Occupational Pesticide Handler Unit Exposure Surrogate Reference Table" (March 2016)
2 Based on proposed label (7969-GUL).
3 Exposure Science Advisory Council Policy #9.1.
4 Inhalation MOE = Inhalation POD (0.02 mg/kg/day) ÷ Inhalation Dose (mg/kg/day).

## 9.2 Short-/Intermediate-Term Post-Application Risk

HED uses the term post-application to describe exposures that occur when individuals are present in an environment that has been previously treated with a pesticide (also referred to as re-entry exposure). Such exposures may occur when workers enter previously treated areas to perform job functions, including activities related to crop production, such as scouting for pests or harvesting. Post-application exposure levels vary over time and depend on such things as the type of activity, the nature of the crop or target that was treated, the type of pesticide application, and the chemical's degradation properties. In addition, the timing of pesticide applications, relative to harvest activities, can greatly reduce the potential for post-application exposure.

### 9.2.1 Dermal Post-application Risk

Occupational Post-application Dermal Exposure

There is no potential hazard *via* the dermal route for dicamba; therefore, a quantitative occupational post-application dermal risk assessment was not completed.

Restricted Entry Interval

The REI specified on the proposed labels is based on the acute toxicity of dicamba. Dicamba is classified as Toxicity Category III via the dermal route, Toxicity Category II for skin irritation potential, and Toxicity Category II for eye irritation. It is not a skin sensitizer. Short- and intermediate-term post-application risk estimates were not a concern on day 0 (12 hours following application) for all post-application activities. Under 40 CFR 156.208 (c) (2) (iii), ai's classified as Acute II for acute dermal, eye irritation or primary skin irritation are assigned a 24-hour REI. Therefore, the [156 subpart K] Worker Protection Statement interim REI of 24 hours is adequate to protect agricultural workers from post-application exposures to dicamba.

### 9.2.2 Inhalation Post-application Risk

There are multiple potential sources of post-application inhalation exposure to individuals performing post-application activities in previously treated fields. These potential sources include volatilization of pesticides and resuspension of dusts and/or particulates that contain pesticides. The agency sought expert advice and input on issues related to volatilization of pesticides from its Federal Insecticide, Fungicide, and Rodenticide Act Scientific Advisory Panel (SAP) in December 2009, and received the SAP's final report on March 2, 2010 (http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2009-0687-0037). The agency has evaluated the SAP report and has developed a Volatilization Screening Tool and a subsequent Volatilization Screening Analysis (http://www.regulations.gov/#!docketDetail;D=EPA-HQ-OPP-2014-0219). During Registration Review, the agency will utilize this analysis to determine if data (i.e., flux studies, route-specific inhalation toxicological studies) or further analysis is required for dicamba.

In addition, the Agency is continuing to evaluate the available post-application inhalation exposure data generated by the Agricultural Reentry Task Force. Given these two efforts, the Agency will continue to identify the need for and, subsequently, the way to incorporate occupational post-application inhalation exposure into the agency's risk assessments.

## 10.0 References

Van Alstine, J., Dicamba: Summary of Hazard and Science Policy Council (HASPOC) Meeting of February 14, 2013: Recommendations on the Requirement of a Subchronic Inhalation Study (TXR No.: 0056589)

Clock-Rust, M, Dicamba: Human-Health Risk Assessment for Proposed Section 3 New Uses on Sweet Corn (D340156)

Savoia, P, Dicamba. Acute and Chronic Dietary Exposure Assessments of Food and Drinking Water to Support the Use of Dicamba on Dicamba-Tolerant Cotton and Soybean for Amended

Section 3 Registration, and Registration of the New N,N-Bis-(3-aminopropyl) methylamine (BAPMA) Salt Formulation. (D408386 & D410346)

Savoia, P, Dicamba. Section 3 Registration for the Amended Use of Dicamba on Dicamba-Tolerant Cotton. Summary of Analytical Chemistry and Residue Data (D408384)

Kamel, A. Dicamba. New use of dicamba on dicamba-tolerant soybean. Petition for establishment of new tolerances for soybean forage and soybean hay. (D384422)

Savoia, P, Dicamba. Bridging Data Demonstrating DGA (diglycolamine), BAPMA (N,N-Bis-(3-aminopropyl) methylamine) and DETA (diethylenetriamine) Salt Product Equivalency, and the Independent Laboratory Validation of the BASF Method Developed for Determining Dicamba Residues in Crops.

Gavelek, A and Lowe, K., Dicamba. Occupational and Residential Exposure Assessment for a Proposed Use on Herbicide-Tolerant Soybean and Cotton. (D429870)

Lang, PL, Historical Control Data for Development and Reproductive Toxicity Studies, Middle Atlantic Reproduction and Teratology Association, Charles River, 1993

Evans, S. and Recore, S., Dicamba: Tier I (Scoping) Review of Human Incidents and Epidemiology (Nov. 10, 2015, D427231)

# Appendix A. Toxicology Profile

## A.1 Toxicology Data Requirements

The requirements (40 CFR 158.340) for food use for dicamba are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

**Table A.1 Toxicology Requirements for Dicamba**

| Guideline Number and Toxicity Study | | Required | Satisfied |
|---|---|---|---|
| 870.1100 | Acute Oral Toxicity | yes | yes |
| 870.1200 | Acute Dermal Toxicity | yes | yes |
| 870.1300 | Acute Inhalation Toxicity | yes | yes |
| 870.2400 | Primary Eye Irritation | yes | yes |
| 870.2500 | Primary Dermal Irritation | yes | yes |
| 870.2600 | Dermal Sensitization | yes | yes |
| 870.3100 | Oral Sub-chronic (Rodent) | yes | yes |
| 870.3150 | Oral Sub-chronic (Non-Rodent) | yes+ | yes |
| 870.3200 | 21-Day Dermal | yes | yes |
| 870.3250 | 90-Day Dermal | CR | -- |
| 870.3465 | 90/28-Day Inhalation | yes | yes |
| 870.3700 | Developmental Toxicity (Rodent) | yes | yes |
| 870.3700 | Developmental Toxicity (Non-rodent) | yes | yes |
| 870.3800 | Reproduction | yes | yes |
| 870.4100 | Chronic Toxicity (Rodent) | yes | yes |
| 870.4100 | Chronic Toxicity (Non-rodent) | no | yes |
| 870.4200 | Oncogenicity (Rat) | yes | yes |
| 870.4200 | Oncogenicity (Mouse) | yes | yes |
| 870.4300 | Chronic/Oncogenicity | yes | yes |
| 870.5100 | Mutagenicity: Gene Mutation - bacterial | yes | yes |
| 870.5395 | Mutagenicity: Cytogenetics | yes | yes |
| 870.5500 | Mutagenicity: Other Genotoxic Effects | yes | yes |
| 870.6100 | Acute Delayed Neurotoxicity (Hen) | no | - |
| 870.6100 | 90-Day Neurotoxicity (Hen) | no | - |
| 870.6200 | Acute Neurotoxicity Screening Battery (Rat) | yes | yes |
| 870.6200 | 90-Day Neurotoxicity. Screening Battery (Rat) | yes | yes |
| 870.6300 | Developmental Neurotoxicity | CR | - |
| 870.7485 | General Metabolism | yes | yes |
| 870.7600 | Dermal Penetration | CR | no |
| 870.7800 | Immunotoxicity | yes | yes |

+ Requirements are satisfied by chronic oral toxicity studies. CR: Conditionally Required

## A.2 Toxicity Profiles

The study NOAELs and LOAELs may not reflect current HED policies, but the updates would not impact endpoint selection or PODs, which are protective of all effects observed in the database.

**Table A.2.1. Acute Toxicity of Dicamba Acid**

| OPPTS Guideline | Study Type | MRID | Results | Toxicity Category |
|---|---|---|---|---|
| 870.1100 | Acute oral toxicity / rat | 00078444 | $LD_{50}$ = > 2740 mg/kg | III |
| 870.1200 | Acute dermal toxicity / rat | 00241584 | $LD_{50}$ = > 2000 mg/kg | III |
| 870.1300 | Acute inhalation toxicity / rat | 00263861 | $LC_{50}$ = > 5.3 mg/L | IV |
| 870.2400 | Primary eye irritation / rabbit | 00241584 | Irritant | II |
| 870.2500 | Primary dermal irritation / rabbit | 00237955 | Irritant | II |
| 870.2600 | Dermal sensitization / guinea pig | 00263861 | Non-Sensitizer | -- |

**Table A.2.2. Acute Toxicity of Dicamba BAPMA Salt**

| Study | MRID | Results | Tox Cat |
|---|---|---|---|
| OPPTS 870.1100-OECD 423<br><br>Acute oral toxicity / rat Bioassay | 48599303 | $LD_{50}$ Females is >2,000 mg/kg<br>One out of six females died on study day 5 after the administration of 2,000 mg/kg. Clinical observations in all six animals revealed impaired general state, dyspnea, piloerection and ataxia from hour 0 until study day 3 after administration. Staggering, reduced feces and exsiccosis were observed in two animals between study day 1 and 3, while gasping was seen only in one animal on study day 1. The animal that died showed red discoloration of the fore stomach. | III |
| OPPTS 870.1200-OECD 402<br><br>Acute dermal toxicity / rat Bioassay | 48599304 | $LD_{50}$ Males /females> 5000 mg/kg<br>No mortality occurred. No signs of systemic toxicity or skin effects were observed. Mean body weight of animals increased within the normal range throughout the study period. No macroscopic pathologic abnormalities were noted in the animals examined at the end of the study. | IV |
| OPPTS 870.1300-OECD 403<br><br>Acute inhalation toxicity / rat | 48599305 | $LC_{50}$ Males/females > 0.557 mg/L<br>(MMAD between 1.2 and 3.8µm, GSD 3.2 to 5.8)<br>No animals died at 0.294 mg/L. All death occurred at 1.052 and 5.045 mg/L. On study days 1-3 or 7-9. Clinical signs included accelerated respiration, labored respiration, intermittent respiration, abdominal respiration, respiration sounds, red encrusted eye, semi-closed eyelid, no defecation, poor general state, high stepping gait, piloerection and substance contaminated fur. In all mortalities body weights decreased until death. Gross pathological abnormalities included dark-red discoloration, lung edema, encrusted nose. | III |

| | | | |
|---|---|---|---|
| OPPTS 870.2400-OECD 405<br><br>Primary eye irritation / rabbit | 48599306 | No corneal opacity or iritis.<br>All eyes positive for conjunctival irritation (chemosis score of 2) at 1 hr; no positive scores for conjunctival irritation at 24 hrs or subsequently (only scores of 1 for redness and/or chemosis). All scores zero by day 7. | IV |
| OPPTS 870.2500-OECD 404<br><br>Primary dermal irritation / rabbit | 48599307 | Not irritating<br>No adverse skin reactions were observed in all animals at any examination term.<br>PII was 0.0. | IV |
| OPPTS 870.2600-OECD 429<br><br>Dermal Sensitization-Local Lymph Node Assay/ mice | 48599308 | Local Lymph Node Assay<br>Ambiguous. Positive control was appropriate.<br>The undiluted test substance caused statistically significant increase in 3H-thymidine incorporation into the cells (increases slightly above S.I. of 3 for $^{3}$H-thymidine incorporation for undiluted material). There was a statistically significant increase in some lymph node weights as well. | Positive |

**Table A.2.3. Acute Toxicity of BAPMA Base [N, N-Bis-(3-aminopropyl)methylamine]**

| Guideline | Study Type | Source | Results | Toxicity Category |
|---|---|---|---|---|
| BASF Test | Acute oral toxicity / rat | MSDS Sheet | $LD_{50}$ = 691 mg/kg | III |
| BASF Test | Acute dermal toxicity / rabbit | MSDS Sheet | $LD_{50}$ = 200 mg/kg | II |
| BASF Test | Acute inhalation toxicity / rat | MSDS Sheet | $LC_{50}$ = 0.07 mg/L | II |
| OECD 404 | Primary eye irritation / rabbit | MSDS Sheet | Corrosive | I |
| QSAR | Primary dermal irritation | MSDS Sheet | Irritant | II |
| OCED 429 | Dermal sensitization / Mouse | MSDS Sheet | Sensitizer | -- |

**Table A.2.4. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid**

| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
|---|---|---|
| 870.3100<br><br>Sub-chronic Oral - Rat | 44623101 (1997)<br>(0, 500, 3000, 6000, 12000 ppm)<br>M:0,40.1,238.7,479.4,1000 mg/kg/day<br>F:0,43.2,266.4,535.6,1065.3 mg/kg/day<br><br>Acceptable/Guideline | NOAEL= 479.4/535.6 mg/kg/day(M/F).<br>LOAEL= 1000/1065.3 mg/kg/day (M/F) based on clinical signs, increased liver weight and increased hepatocyte hypertrophy and hepatocellular pigmentation. |
| 870.3200<br><br>21-Day Dermal Study- Rabbits | 40547901 (1986)<br>0, 40, 200 and 1000 mg/kg/day as a 42.0% Dicamba formulation<br>(Lot No. 52410301)<br>Supplementary | Systemic NOAEL > 1000 mg/kg/day: Dermal NOAEL = 40 mg/kg/day & LOAEL = 200 mg/kg/day (fissuring, acanthosis and hyperkertosis). At 1000 mg/kg/day - desquamation, moderate erythema, edema and atonia, fissuring, acanthosis and hyprkeratosis. Classified minimum. |

| Table A.2.4. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid | | |
|---|---|---|
| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
| 870.3200<br><br>28-Day dermal toxicity-Rat | 45814501 (2002)<br>0, 30, 300, 1000 mg/kg/day (M/F)<br><br>Acceptable/Guideline | NOAEL= 1000 mg/kg/day (HDT)<br>LOAEL= not determined. |
| 870.3465<br>28-Day Inhalation Toxicity- Rat | 49461101 (2014)0, 0.001, 0.005, 0.050 mg/L<br>Acceptable/Guideline | NOAEL=0.005/0.005 mg/L (M/F)<br>LOAEL=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females |
| 870.3700a<br><br>Prenatal developmental - Rat | 00084024 (1981)<br>0,64,160,400 mg/kg/day (GD 6-19)<br><br>Acceptable/Guideline | **Maternal**:<br>NOAEL= 160 mg/kg/day;<br>LOAEL= 400 mg/kg/day based on increased mortality, clinical signs (ataxia, stiffening of body when touched, decreased motor activity) and decreased food consumption.<br>**Developmental**:<br>NOAEL= 400 mg/kg/day (HDT),<br>LOAEL not established. |
| 870.3700b<br><br>Prenatal developmental - New Zealand White Rabbit | 42429401 (1992)<br>0, 30, 150, 300 mg/kg/day (GD 6-18)<br><br>Range-finding study:<br>0, 62.5, 125, 250, 500 mg/kg/day (GD 6-18)<br><br>Acceptable/Guideline | **Maternal**:<br>NOAEL= 62.5 mg/kg/day,<br>LOAEL= 150 mg/kg/day based on increased abortion, clinical signs (decreased motor activity, ataxia).<br>**Developmental**:<br>NOAEL= 62.5 mg/kg/day,<br>LOAEL= 150 mg/kg/day based on increased abortion at gestation day 22 (1 in 20 does), after dosing ceased on day 18 |
| 870.3800<br><br>Reproduction and fertility effects - Rat | 43137101 (1993)<br>(0,500,1500,5000 ppm)<br>M: 0,40,122,419 mg/kg/day<br>F: 0,45, 136, 450 mg/kg/day<br><br>Acceptable/Guideline | **Parental/Systemic:**<br>NOAEL= 122/136 mg/kg/day (M/F)<br>LOAEL= 419/450 mg/kg/day (M/F) based on clinical signs (slow righting reflex).<br>**Reproductive:**<br>NOAEL=122 mg/kg/day<br>LOAEL= 419 mg/kg/day based on delayed sexual maturation in F1 males.<br>**Offspring:**<br>NOAEL=136 mg/kg/day<br>LOAEL= 450 mg/kg/day based on decreased pup weights in the F1 generation at PND0/PND21 and F2B generation at PND21, relative to the MARTA historical control database.<br>Classified minimum |

| Table A.2.4. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid | | |
|---|---|---|
| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
| 870.4200a<br><br>Chronic Toxicity/ Carcinogenicity -Rat | 00146150 (1985)<br>(0,50,250,2500 ppm)<br>M: 0,2,11,107 mg/kg/day<br>F: 0,3,13,127 mg/kg/day<br><br>Acceptable/Guideline | NOAEL= 107/127 mg/kg/day (M/F)<br>LOAEL was not established. Brain ventricular dilation in females at the highest dose, but not observed in other studies.<br>Not carcinogenic.<br>The study is considered adequate for evaluating the carcinogenic potential. |
| 870.4100b<br><br>Chronic toxicity - Dog | 40321102 (1986)<br>(0,100,500,2500 ppm)<br>0,2,11,52 mg/kg/day<br><br>Acceptable/Guideline | NOAEL=52 mg/kg/day (HDT)<br>LOAEL= Not Achieved |
| 870.4200b<br><br>Carcinogenicity - Mouse | 40872401 (1988)<br>(0,50,150,1000,3000 ppm)<br>M: 0,5.5,17.2,108,358 mg/kg/day<br>F: 0,5.8,18.8,121,354 mg/kg/day<br><br>Acceptable/Guideline | NOAEL=358/354 mg/kg/day (M/F),<br>LOAEL was not established.<br>Not carcinogenic.<br>The study is considered adequate for evaluating the carcinogenic potential. |
| 870.5100<br><br>Gene Mutation Salmonella Typhimurium | 00143001 (1979)<br><br>Acceptable/Guideline | Negative, not mutagenic. |
| 870.5395<br><br>Chromosome Aberration (CHO) | 40321101 (1986)<br><br>0, 2330, 1170, 590, and 300 µg/mL<br>Acceptable/Guideline | Negative, chromosome aberrations were not induced in a cultured CHO cells at concentrations tested either with or without S-9 activation. |
| 870.5550<br><br>Unscheduled DNA Synthesis (UDS) | 00143001 (1979)<br><br>Acceptable/Guideline | Negative, no evidence of UDS at levels 0.1 to 3000 µg/mL. |
| 870.6200<br><br>Acute Neurotoxicity-Rat | 42774104 (1993)<br>0,300,600,1200 mg/kg<br><br>Acceptable/Guideline | NOAEL was not established,<br>LOAEL=300 mg/kg based on severe neurological signs (impaired respiration, rigidity upon handling, prodding, or dropping, impaired gait and righting reflex in both sexes. |
| 870.6200<br><br>Sub-chronic Neurotoxicity-Rat | 43245210 (1994)<br>0,3000,6000,12000 ppm<br>M:0,197.1,401.4,767.9 mg/kg/day<br>F: 0,253.4,472.0,1028.9 mg/kg/day<br><br>Acceptable/Guideline | NOAEL= 401.4/472.0 mg/kg/day (M/F);<br>LOAEL= 767.9/1028.9 mg/kg/day (M/F) based on rigidity body tone, slightly impaired righting reflex and gait. |

| Table A.2.4. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Acid | | |
|---|---|---|
| Guideline No./ Study Type/ | MRID Nos. Doses/Classification | Results |
| 870.3100 and 870.6200<br><br>Combined Sub-chronic Toxicity / Sub-chronic Neurotoxicity Study-Rat | 48358001 (2011)<br><br>0, 500, 3000, 6000, 12000 ppm<br>M: 0, 34, 197, 397, 803 mg/kg/day<br>F: 0, 39, 230, 458, 938 mg/kg/day<br>Crl:CD® [SD] rats<br><br>Acceptable/Guideline | NOAEL = 397/458 mg/kg/day (M/F)<br>LOAEL = 803/938 mg/kg/day (M/F) based on behavioral signs (uncoordinated righting, decreased hindlimb foot splay, unkempt appearance, gasping, rales in males and impaired equilibrium, rigid muscle tone in females) |
| 870.7485<br><br>Metabolism | 44609801 (1998)<br>Acceptable/Non-guideline<br><br>46022302 (2003)<br>Acceptable/Non-guideline<br><br>46022303 (2003)<br>Acceptable/Non-guideline<br><br>00028261(1967)<br>Acceptable/guideline | Rapidly absorbed and rapidly excreted in urine and feces. Dicamba is not metabolized or bioaccumulation. Approximately 13% of dicamba in the urine is conjugated as the glucuronide. |
| 870.7800<br><br>Immunotoxicity - Rat | 48081601 (2010)<br><br>0, 500, 1500, or 4000 ppm<br>(0, 37, 108, or 307 mg/kg/day)<br><br>Acceptable/Guideline | Negative for immunotoxicity<br><br>The NOAEL for immunotoxicity and systemic toxicity is 307 mg/kg/day<br><br>LOAEL is undetermined |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type Chemical | MRID (year) | Results |
| 870.1100<br><br>DCSA Acute Oral Toxicity | 47899504 (2007)<br><br>Acceptable/Guideline | $LD_{50}$ = 2641 mg/kg<br><br>wobbly gait at 2000 mg/kg |
| 870.1100<br><br>DCGA Acute Oral Toxicity | 47899505 (2009)<br><br>Acceptable/Guideline | $LD_{50}$ = 1460 mg/kg |
| 870.3050<br><br>DCGA Subchronic Tox - Rat (28 days) | 47899506 (2009)<br><br>0, 500, 3000, 6000, 12000 ppm<br>M: 0, 40, 240, 474, 956 mg/kg/day<br>F: 0, 45, 265, 519, 1063 mg/kg/day for females.<br><br>Acceptable/Guideline | Included FOB and motor activity<br>NOAEL = 474 mg/kg/day<br>LOAEL = 956 mg/kg/day based upon decreased BW in males |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type<br>Chemical | MRID<br>(year) | Results |
| 870.3100<br><br>DCSA<br>Subchronic Tox<br>- Rat (90 days) | 47899507 (2009)<br><br>(0, 500, 3000, 6000, 12000 ppm).<br>M: 0, 32, 195, 362, 659 mg/kg/day<br>F: 0, 37, 222, 436, 719 mg/kg/day<br><br>Crl:CD®[SD] rats<br><br>Acceptable/Guideline | Included FOB and MA.<br>NOAEL = 362 mg/kg/day<br>LOAEL = 659 mg/kg/day based on decreased body weight, increased motor activity, decreased hematological parameters (i.e. RBC count), and increased serum liver enzymes |
| 870.3100<br><br>Dicamba BAPMA<br>90-Day Toxicity Study-Rat | 49441801 (2014)<br><br>M: 0, 257, 513, 1027 mg/kg/day<br>F: 0, 294, 589, 1178 mg/kg/day<br><br>Acceptable/Guideline | NOAEL is 513/589 mg/kg/day (M/F) (357/409 as Acid form)<br>LOAEL is 1027/1178 mg/kg/day (M/F) (714/819 as Acid Form), based on altered hematology, kidney effects, increased clotting time and clinical chemistry parameters |
| 870.3150<br><br>DCSA<br>Subchronic Tox – Dog (90 days) | 48358002 (2011)<br><br>0, 15, 50 and 150 mg/kg/day 90-day capsule study.<br><br>Acceptable/Guideline | NOAEL = 50 mg/kg/day<br>LOAEL = 150 mg/kg/day based on mortality, decreased body weight, clinical signs (abnormal excreta and emesis), and increased clotting time. |
| 870.3200<br><br>Dicamba DGA<br>21-Day Dermal Study--Rabbits | 43554206<br><br>Diglycolamine salt (DGA, 59%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day<br><br>Acceptable/Guideline | NOAEL = 1000 mg/kg/day (Limit-Dose) for dermal irritation and systemic toxicity.<br>LOAEL: not established for either end-point. |
| 870.3200<br><br>Dicamba IPA<br>21-Day Dermal Study--Rabbits | 43554207<br><br>Isopropylamine salt (IPA, 41%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week<br><br>Acceptable/Guideline | NOAEL = 1000 mg/kg/day (Limit-Dose) for dermal irritation and systemic toxicity.<br>LOAEL: not established for either end-point. |
| 870.3465<br><br>Dicamba BAPMA<br>28-Day Inhalation Toxicity Study-Rats | 49441803 (2014)<br><br>0, 0.0014, 0.0070, 0.00352 mg/L<br><br>Acceptable/Guideline | NOAEL=NA<br>LOAEL=0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia in the larynx |
| 870.3650<br><br>BAPMA Base<br>OECD 422 Developmental-Reproduction Screening Test | NA | NOAEL: 25 mg/kg/day<br>LOAEL: 100 mg/kg/day based on decreased motor activity and decreased water consumption<br><br>At 500 mg/kg/day excessive toxicity and dam deaths |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type<br>Chemical | MRID<br>(year) | Results |
| 870.3700a<br><br>DCSA<br><br>Developmental<br>- Rat | 47899519 (2007)<br><br>0, 10, 30, 100 mg/kg/day (GD 6-19). Crl:CD(SD) rats<br><br><br>47899518<br>(range-finding study) | **Maternal**<br>NOAEL: 100 mg/kg/day, highest dose tested<br>LOAEL: not attained<br>**Developmental**<br>NOAEL: 100 mg/kg/day, highest dose tested<br>LOAEL: not attained<br>Classified acceptable/guideline when considered with range-finding study.<br><br>Range-finding study: MRID 47899518.<br>0, 50, 200, 500 or 1000 mg/kg/day: 8 females/dose<br>200 mg/kg/day: clinical signs (rales, red/clear material on body), decreased fetal weight<br>500 mg/kg/day: mortality, early resorptions in all survivors |
| 870.3700a<br><br>DCGA<br>Developmental<br>Rat Range-finding study | 47899520 (2009)<br><br>0, 50, 200, 500, 1000 mg/kg/day<br><br>Acceptable/Guideline | **Maternal**:<br>NOAEL: 50 mg/kg/day<br>LOAEL: 200 mg/kg/day based on signs of rales, clear material on body<br><br>At 500 mg/kg/day: BW 4.0-6.6% lower GD 13-20<br>At 1000 mg/kg/day: Mortality. BW 4.4-12.1% lower GD 12-20<br>**Developmental:**<br>No effects on uterine growth, survival, external malformations or variations. Fetuses received external exam only, no skeletal examination. |
| 870.3700a<br><br>Dicamba BAPMA<br>Developmental Toxicity<br>Study-Rats | 49441802 (2014)<br><br>0, 29, 86, 288 mg/kg/day<br><br>Acceptable/Guideline | **Maternal**<br>NOAEL is 29 mg/kg/day in dams<br>(20 as Acid form)<br>LOAEL is 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions<br>(60 as Acid Form)<br>**Developmental**<br>NOAEL > 288 mg/kg/day<br>(200 as acid equivalent) |
| 870.3700b<br><br>DCSA<br>Developmental<br>- Rabbit | 47899522 (2009)<br><br>0, 10, 25, 65 mg/kg/day (GD 6-28). NZW rabbits<br><br>47899521 (2010)<br>Range-finding study<br><br>0, 10, 30, 100, 300 mg/kg/day<br><br>Acceptable/Guideline | **Maternal**<br>NOAEL: 65 mg/kg/day, highest dose tested.<br>LOAEL: not attained<br>**Developmental**<br>NOAEL: 65 mg/kg/day, highest dose tested.<br>LOAEL: not attained<br>Classified acceptable/guideline when considered with range-finding study.<br><br>Range-finding study: MRID 47899521<br>6 females/dose. 300 mg/kg/day was lethal dose |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type<br>Chemical | MRID<br>(year) | Results |
| 870.3800<br><br>DCSA<br>Reproduction and fertility effects<br>- Rat | 47899517 (2009)<br><br>0, 50, 500, 5000 ppm<br>M: 0, 4, 37, 362 mg/kg/day<br>($F_0$ generation)<br>F: 0, 4, 43, 414 mg/kg/day<br>($F_0$ generation)<br>Crl:CD(SD) rats<br><br><br>Acceptable/Guideline | **Parental**<br>NOAEL = 37 mg/kg/day<br>LOAEL = 362 mg/kg/day based upon decreased body weight.<br>**Reproduction**<br>NOAEL = 362 mg/kg/day, highest dose tested.<br>LOAEL: Not attained.<br>**Offspring**<br>NOAEL = 4 mg/kg/day<br>LOAEL = 37 mg/kg/day based upon decreased pup body weight in $F_1$ pups on postnatal days 14 and 21 during lactation and week 18 in females.<br>At 5000 ppm, high incidence of pup mortality |
| 870.4200a<br><br>DCSA<br>Chronic Toxicity/<br>Carcinogenicity<br>-Rat | 47899516 (2009)<br><br>48358003 (2011)<br><br>(0, 10, 100, 300, 1000, 3000 ppm)<br>M: 0.5, 5.0, 14.6, 48.8, and 150.1 mg/kg/day<br>F: 0.6, 6.1, 18.4, 60.9, and 181.5 mg/kg/day<br>Crl:CD®[SD] rats<br><br>Acceptable/Guideline | NOAEL = 150 mg/kg/day, highest dose tested. Not carcinogenic.<br>LOAEL: Not established |
| 870.5100<br><br>DCSA Bacterial gene mutation | 47899509<br><br>Acceptable/Guideline | Negative, did not induce gene mutation |
| 870.5100<br><br>DCGA Bacterial gene mutation | 47899514<br><br>Acceptable/Guideline | Negative, did not induce gene mutation |
| 870.5100<br><br>Dicamba Acid<br>Bacterial gene mutation | 47899525<br><br>Acceptable/Guideline | Negative, did not induce gene mutation |
| 870.5100<br><br>Dicamba BAPMA<br>Bacterial gene mutation | 48718001<br><br>Acceptable/Guideline | Negative |
| 870. 5300<br><br>DCSA HGPRT in Chinese hamster cells | 47899512<br><br>Acceptable/Guideline | Negative, did not induce forward mutations at the HGPRT locus in CHO cells |
| 870. 5300<br><br>Dicamba Acid HGPRT in Chinese hamster cells | 47899526<br><br>Acceptable/Guideline | Negative, did not induce forward mutations at the HGPRT locus |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type<br>Chemical | MRID<br>(year) | Results |
| 870.5300<br><br>Dicamba BAPMA<br>HGPRT in Chinese hamster cells | 48718002<br><br>Acceptable/Guideline | Negative |
| 870.5375<br><br>DCSA Chromosome aberration assay in human lymphocytes | 47899510<br><br>Acceptable/Guideline | No conclusions can be reached; the data are inconclusive. |
| 870.5375<br><br>Dicamba Acid<br>Chromosomal aberration assay in human lymphocytes | 47899527<br><br>Acceptable/Guideline | Positive, the S9-activated portion of the assay should have been repeated |
| 870.5375<br><br>Dicamba BAPMA<br>Chromosomal aberration assay in human lymphocytes | 48718003<br><br>Acceptable/Guideline | Positive, clastogenic +/- S9 fraction |
| 870.5385<br><br>DCSA<br>Chromosome aberration assay in rat bone marrow | 47899513<br><br>Acceptable/Guideline | Negative, did not cause an increase in the number of chromosome aberrations in rat bone marrow cells |
| 870.5385<br><br>DCGA<br>Chromosome aberration assay in rat bone marrow | 47899515<br><br>Acceptable/Guideline | Negative, did not cause increased numbers of chromosome aberrations in rat bone marrow cells |
| 870.5395<br><br>DCSA<br>Micronucleus assay in mice | 47899511<br>0, 250, 500, and 1000 mg/kg by gavage (corn oil)<br><br>Range-finding study:<br>0, 500, 1000, and 2000 mg/kg<br><br>Acceptable/Guideline | Negative, did not induce a clastogenic or aneugenic response in mouse bone marrow cells of male mice<br><br>At doses above 1000 mg/kg, hypo-activity, squinted eyes, hunched posture clinical signs |
| 870.5395<br><br>Dicamba Acid<br>Micronucleus assay in mice | 47899528<br>0, 250, 500, and 1000 mg/kg by gavage (corn oil)<br><br>Acceptable/Guideline | Negative, was neither clastogenic nor aneugenic in mouse bone marrow<br><br>At doses of 250 mg/kg or more, slight hypo-activity and ataxia were observed |
| 870.5395<br><br>Dicamba BAPMA<br>Micronucleus assay in mice | 48718004<br>0, 500, 1000 and 2000 mg/kg by gavage (water)<br><br>Acceptable/Guideline | Negative, is neither clastogenic nor aneugenic up to the limit dose in vivo in mice<br><br>At doses of 500 mg/kg or more, hunched posture and reduced general condition were observed |

| Table A.2.5. Sub-chronic, Chronic and Other Toxicity Profile for Dicamba Metabolites and BAPMA Salt | | |
|---|---|---|
| Study Type<br>Chemical | MRID<br>(year) | Results |
| 870.7485<br><br>DCSA Metabolism<br>(single dose) | 47899502 (2006)<br><br>100 mg/kg | Extensively absorbed and excreted rapidly in urine with little metabolism. |
| 870.7485<br><br>DCSA Metabolism<br>(repeated doses) | 47899503 (2006)<br><br>(42, 125, 250, 375, or 500 mg/kg/day<br>Acceptable/Guideline | Well absorbed and rapidly excreted in urine with minimal metabolism. |

| Table A.2.6. Dicamba BAPMA Salt Toxicity: Comparison to Dicamba Acid and DCSA Metabolite | | | |
|---|---|---|---|
| Study | Dicamba Acid<br>NOAEL/LOAEL | Dicamba BAPMA Salt<br>NOAEL/LOAEL | DCSA Metabolite<br>NOAEL/LOAEL |
| 90-Day Oral Rat | NOAEL= 479.4/535.6 mg/kg/day (M/F)<br>LOAEL= 1000/1065.3 mg/kg/day (M/F), based on clinical signs, decreased BWG, increased liver weight, increased hepatocyte hypertrophy and hepatocellular pigmentation. | NOAEL is 513/589 mg/kg/day (M/F) (357/409 as Acid form)<br>LOAEL is 1027/1178 mg/kg/day (M/F) (714/819 as Acid Form), based on altered hematology and clinical chemistry parameters | NOAEL is 362 mg/kg/day<br>LOAEL is 659 mg/kg/day, based on decreased BW, increased motor activity, decreased hematological parameters, increased liver enzymes |
| Rat Developmental Study | **Maternal**<br>NOAEL = 160 mg/kg/day<br>LOAEL = 400 mg/kg/day in dams, based on mortality, ataxia, decreased motor activity<br><br>**Developmental**<br>NOAEL > 400 mg/kg/day | **Maternal**<br>NOAEL is 29 mg/kg/day in dams (20 as Acid form)<br>LOAEL is 86 mg/kg/day in dams, based on ataxia, unsteady gait and convulsions (60 as Acid Form)<br>**Developmental**<br>NOAEL > 288 mg/kg/day (200 as acid equivalent) | **Maternal**<br>NOAEL > 100 (HDT) in dams<br>**Developmental**<br>NOAEL > 100 (HDT)<br><br>Range Finding Study:<br>At 200 mg/kg/day there was decreased fetal weight and mortality/early resorptions at 500 mg/kg/day |
| Rat Reproduction Study | **Parental/Systemic:**<br>NOAEL= 122/136 mg/kg/day (M/F)<br>LOAEL= 419/450 mg/kg/day (M/F) based on clinical signs (slow righting reflex).<br>**Reproductive:**<br>NOAEL=122 mg/kg/day;<br>LOAEL= 419 mg/kg/day based on delayed sexual maturation in F1 males.<br>**Offspring:**<br>NOAEL=136 mg/kg/day<br>LOAEL= 450 mg/kg/day based on impaired pup growth | **BAPMA Base Cation**<br>OECD 422 Reproduction Study<br><br>NOAEL: 25 mg/kg/day<br>LOAEL: 100 mg/kg/day based on decreased motor activity and water consumption<br><br>At 500 mg/kg/day dam deaths | **Parental**<br>NOAEL = 37 mg/kg/day<br>LOAEL = 362 mg/kg/day based upon decreased body weight.<br>**Reproductive**<br>NOAEL = 362 mg/kg/day (HDT)<br>LOAEL: Not attained.<br>**Offspring**<br>NOAEL = 4 mg/kg/day<br>LOAEL = 37 mg/kg/day based upon decreased pup body weight in $F_1$ pups on postnatal days 14 and 21.<br>At 5000 ppm, high incidence of pup mortality |

| | | | |
|---|---|---|---|
| | (decreased pup weights) in the F1 and F2B generations during lactation period. | | |
| 28-Day Inhalation Study | NOAEL=0.005/0.005 mg/L (M/F) LOAEL=0.050/0.050 mg/L (M/F), based on minimal multifocal bronchiole-alveolar hyperplasia in males; multiple microscopic findings in the lung and associated lymph nodes in females | NOAEL=NA LOAEL=0.0014 mg/L (LDT), based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasia in the larynx | NA |

## A.3 Hazard Identification and Endpoint Selection

### A.3.1 Acute Reference Dose (aRfD) - Females age 13-49

Study Selected: An acute endpoint for women of childbearing age was not selected because there were no developmental effects attributed to an acute exposure. There was no developmental toxicity in the developmental rabbit study with DCSA, in the developmental rat study with dicamba, or in the main developmental rat study with DCSA. In the range finding rat study with DCSA, early resorptions occurred, but this effect was only at a dose that was lethal to dams. In the developmental rabbit study with dicamba, there was one abortion out of 20 does (gestation day 22), but this was after last day of dosing at a dose where the majority of does were showing signs of neurotoxicity. Therefore, the endpoint of neurotoxicity selected for the general population will be protective of potential offspring effects.

### A.3.2 Acute Reference Dose (aRfD) - General Population: Dicamba and Dicamba BAPMA

Study Selected: Rat Developmental Toxicity – Dicamba BAPMA

MRID No.: 49441802

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: NOAEL = 29 mg/kg/day. Neurological signs such as ataxia, unsteady gait and convulsions at LOAEL = 86 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: These effects are considered a single-dose effect since the signs occurred shortly after dosing. This study was selected because it represents the most sensitive endpoint in the dicamba database for exposure to the parent dicamba acid or its BAPMA salt demonstrating an acute response with a well-defined NOAEL value. The dicamba BAPMA study NOAEL will be protective of the effects of dicamba acid via the oral route. The decreased body weights observed in the dicamba acid or DCSA reproduction studies were considered to be the result of multiple doses and not an acute effect, thus those studies were not appropriate for this scenario. The ACN study was considered for this scenario with a LOAEL of 300 mg/kg, however the study did not have a NOAEL value and with a 10X $UF_L$ applied to this LOAEL would result in a similar POD of 30 mg/kg. The selected POD will be protective of the

effects of dicamba acid and the BAPMA salt via the oral route. A separate acute dietary assessment for females 13-49 was not performed since no there was no developmental toxicity attributed to a single dose in the toxicology data base. The abortions in the rabbit developmental study at the LOAEL occurred at gestation day 22 or later. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain an aPAD of 0.29 mg/kg/day.

### A.3.3 Chronic Reference Dose (cRfD): Dicamba and Dicamba BAPMA

Study Selected: Reproductive study in rats with DCSA.

MRID No.: 47899517

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: Offspring NOAEL = 4 mg/kg/day based on decreased F1 pup weight at Offspring LOAEL = 37 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was decreased pup weight in the F1 generation on postnatal days 14 and 21 (both sexes) and week 18 in females. This study had the lowest NOAEL in the database for dietary exposure to the DCSA metabolite. The NOAEL for decreased pup weight in the reproduction study with dicamba was used as point of departure in previous risk assessments (NOAEL = 45 and LOAEL = 136 mg/kg/day) for conventional crops. However, the DCSA study is more appropriate to use since people are mainly exposed to DCSA in food derived from the dicamba-tolerant crops which generate DCSA. This endpoint is protective of neurotoxicity findings in the other studies with both dicamba and DCSA, which occurred at much higher doses. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF) is applied to the NOAEL to obtain a cPAD of 0.04 mg/kg/day.

### A.3.4 Incidental Oral Exposure (Short- and Intermediate-Term): Dicamba and Dicamba BAPMA

Study Selected: Reproductive study in rats with dicamba.

MRID No.: 43137101

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: Offspring NOAEL = 136 mg/kg/day based on decreased F1 and F2B pup weights at an Offspring LOAEL = 450 mg/kg/day.

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was decreased pup weight in F1 and F2B generations of the dicamba acid reproduction study. The toxicology studies on the plant metabolites are not appropriate for this scenario since these metabolites are generated inside the plants and unavailable for incidental oral exposure. The developmental studies are not

appropriate for incidental oral scenarios involving hand-to-mouth behavior. The dicamba BAPMA salt has no residential uses where this scenario occurs. The dicamba acid sub-chronic oral study in adult rats had a NOAEL of 479.4 mg/kg/day and a LOAEL of 1000 mg/kg/day and didn't provide the most sensitive POD for the incidental oral scenario life stage. Consequently, the most appropriate study was the multi-generation reproductive toxicity study in rats dosed with parent compound was selected based on impaired pup growth at 450 mg/kg/day (LOAEL); the NOAEL of 136 mg/kg/day was selected as the POD for this scenario. This POD will be protective of neurotoxicity in the other studies which occurred at higher doses. It is appropriate to use the reproduction study with dicamba, and not DCSA, because the population of concern, children, will be exposed mainly to dicamba through hand-to-mouth behaviors, and not to DCSA, which is not a mammalian metabolite. The DCSA metabolite is primarily present in dicamba-tolerant plants and not expected to be a concern for incidental oral scenarios. An uncertainty factor of 100X (10X to account for interspecies extrapolation, 10X for intraspecies variation, and an FQPA factor of 1X).

### A.3.5 Dermal Exposure (Short-, Intermediate- and Long-Term)

Dermal assessments will not be performed for dicamba or dicamba BAPMA salt since the dermal studies for the dicamba, IPA and DGA salts all had NOAELs of 1000 mg/kg/day. The dicamba anion component is ~80% of the dicamba BAPMA salt weight, so the BAPMA composition is unlikely to significantly influence the dermal toxicity.

### A.3.6 Inhalation Exposure (Short-, Intermediate- and Long-Term)

**Dicamba**
Study Selected: Dicamba Inhalation Study

MRID No.: 49461101

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: NOAEL = 0.005 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in males with multiple microscopic findings in the lung and associated lymph nodes in females at a LOAEL = 0.05 mg/L.

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was local respiratory effects which is protective of neurotoxicity in the other studies occurred at much higher doses. The dicamba inhalation study is appropriate to use since workers will be exposed to dicamba via the respiratory route.

**Dicamba BAPMA Salt**
Study Selected: Dicamba BAPMA Inhalation Study

MRID No.: 49441803

Executive Summary: See Appendix A

Dose and Endpoint for Risk Assessment: NOAEL = NA based on ulcers and hyperplasia of the larynx at a LOAEL = 0.0014 mg/L.

Comments about Study/Endpoint/Uncertainty Factors: The endpoint was local respiratory effects which is protective of neurotoxicity in the other studies occurred at much higher doses. The dicamba BAPMA inhalation study is appropriate to use since workers will be exposed to dicamba BAPMA via the respiratory route.

The standard interspecies extrapolation UF can be reduced from 10X to 3X for dicamba acid and BAPMA salt due to the calculation of human equivalent concentrations (HECs) accounting for pharmacokinetic (not pharmacodynamic) interspecies differences. Therefore, the LOC for dicamba acid inhalation exposures is for MOEs less than 30 (3X for interspecies extrapolation, 10X for intraspecies variation, and 1X for FQPA SF when applicable). For BAPMA salt, an additional 10X $UF_L$ is applied due to lack of a study NOAEL. Therefore, the LOC for BAPMA salt inhalation exposures is for MOEs less than 300.

## A.4 Executive Summaries for Dicamba, Dicamba Metabolites and Dicamba Salts

### A.4.1 Sub-chronic Toxicity

#### 870.3100 90-Day Oral Toxicity - Rat

In a 13-week sub-chronic toxicity study (MRID 44623101), dicamba technical (89.4% a.i.) was administered to HanIbm:WIST (Wistar) rats (10 or 20 rats/sex/dose) by feeding at dose levels of 0, 500, 3000, 6000, or 12,000 ppm (equivalent to 0/0, 40.1/43.2, 238.7/266.4, 479.4/535.6, or 1000.0/1065.3 mg/kg/day [M/F]) for 13 weeks. Following 13 weeks of treatment, 10 rats/sex/dose were sacrificed. Rats (10/sex) in the control and 12,000 ppm groups were maintained for a 4-week recovery period to determine the reversibility of effects.

No treatment-related deaths were observed in any treatment group. The liver was the target organ, as evidenced by microscopic liver changes associated with clinical serum chemistry changes and increased relative (to body) liver weights (↑20-23%) in both sexes at the high dose. The livers of the 12,000 ppm females exhibited slight centrilobular hepatocyte hypertrophy (4/10) and an increased incidence of minimal to moderate hepatocellular pigmentation (5/10). Both sexes exhibited increased alkaline phosphatase (↑62-76%), serum alanine aminotransferase (↑59-66%), and serum aspartate aminotransferase (↑29%) activities compared to the controls. Females exhibited an increase in mean gamma glutamyl transferase activity (↑136%) while males showed a decrease activity (↓50%) compared to the controls.

Other effects observed in the 12,000 ppm rats were transient hypothermia (weeks 1-4), reduced activity, slower movements, decreased food consumption, and less efficient food utilization than the controls throughout the treatment period. Lower mean final body weights (↓18-20%), body weight gains (↓28-40%) and adipose tissue content were observed compared to the controls. Decreases in protein (↓10-15%) and globulin (↓16-26%) levels were observed in both sexes. In

females, decreased mean hemoglobin concentration (↓4%) and red blood cell counts (↓4%), and decreased mean corpuscular hemoglobin concentration (↓3%) were observed. Significant ($p<0.05$ or $p<0.01$) increases of white blood cell count (↑13%) and lymphocyte count (↑33%) were observed in 12000 ppm females compared to the controls. Males had a lower mean platelet count (↓7%) and shorter partial thromboplastin time (↓11%) compared to the controls. Urinalysis showed that males excreted more triple phosphate crystals in the 12000 ppm group, whereas females excreted more uric acid crystals in the 12000 and 6000 ppm groups at week 12. Following a 4-week recovery period, all observed effects were recovered.

**The LOAEL for this study is 12,000 ppm (1000 mg/kg/day), based on clinical signs, reduced body weight gains, hematological and clinical serum chemistry changes in both sexes, centrolobular hepatocyte hypertrophy and hepatocellular pigmentation in females, and increased relative (to body) liver weights for both sexes. The NOAEL is 6000 ppm (479 mg/kg/day).**

**870.3100 90-Day Oral Toxicity - Mouse**

NA

**870.3150 90-Day Oral Toxicity - Dog**

NA- See chronic dog study

**870.3200 21/28-Day Dermal Toxicity – Rat**

In a 28-day dermal toxicity study (MRID 45814501), Dicamba (91.0% a.i., batch #B2826511) was applied to the shaved skin of 10 male and 10 female Alpk:AP $_f$SD rats /sex/dose at dose levels of 0, 30, 300 or 1000 mg/kg bw/day, 6 hours/day for 5 days/week during a 28-day period.

Clinical observations, body weights and food consumption were measured throughout the study. Urine samples were taken for clinical pathology during week 4 of the study. A functional observational battery of all animals consisting of: detailed clinical observations, including quantitative assessments of landing foot splay, sensory perception and muscle weakness, and assessment of motor activity was performed on day 22. At the end of the scheduled period, the animals were killed and subjected to a post mortem examination. Blood samples were taken for clinical pathology, selected organs and specified tissues were taken for subsequent histopathological examination.

There were no changes indicative of systemic toxicity in either sex. There were no compound related effects in mortality, clinical signs, body weight, food consumption, hematology, clinical chemistry, organ weights, or gross and histologic pathology. Histopathological changes indicative of irritation were seen in skin from the application site in both sexes given 1000 or 300 mg/kg/day and in some males given 30 mg/kg/day. **A LOAEL for systemic toxicity was not established. The NOAEL is 1000 mg/kg/day the highest dose tested.**

This 28-day dermal toxicity study in the rat is **acceptable/ guideline**, and satisfies the guideline requirement for a 28-day dermal toxicity study (OPPTS 870.3200; OECD 410) in the rat.

**21/28-Day Dermal Toxicity – Rabbit (870.3200)**

In a 21-day dermal study (MRID 40547901), New Zealand white rabbits (5/sex/group) received 15 repeated dermal applications of Dicamba in deionized water at dose levels of 0, 40, 200, or 1000 mg/kg/day, 6 hours/day, 5 days/week over a three week period. No systemic toxicity was observed at any dose level. Dose-related dermal irritation was observed at the application sites. Desquamation was seen predominantly in the 1000 mg/kg/day group while moderate erythema, moderate edema and atonia were observed exclusively in the 1000 mg/kg/day group. A dose-related incidence of fissuring was noted in the 200 and 1000 mg/kg/day groups. The severity of acanthosis and the incidence of hyperkeratosis was increased at these sites in rabbits at 200 and 1000 mg/kg. **For systemic toxicity, the NOAEL was 1000 mg/kg/day (HDT); a systemic LOAEL was not be established.**
This 28-day dermal toxicity study in the rat is **acceptable/ guideline**, and satisfies the guideline requirement for a 21-day dermal toxicity study (OPPTS 870.3200; OECD 410) in the rabbit.

**870.3465 90-Day Inhalation – Rat**

In a nose-only inhalation toxicity study (MRID 49461101), four groups of Crl:WI(Han) rats (10/sex/group; ~7 weeks of age) were administered BAS 183 H [93.9% (Batch No. 0002B01BA-251)] as a dust aerosol at exposure concentrations of 0, 0.001, 0.005, or 0.050 mg/L for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on food consumption, hematology, clinical chemistry, or during ophthalmological examinations. Body weight was not adversely affected.. At 0.05 mg/L, lung weight was statistically increased in both sexes, and the following lung histological lesions were increased in incidence (# affected/10 in treated vs controls) in both sexes: (i) minimal to slight alveolar histiocytosis (10 vs 4 in males; 10 vs 1 in females); (ii) minimal macrophage aggregates ( 6 vs 0 in males; 8 vs 0 in females); (iii) minimal to slight bronchial hypertrophy/hyperplasia (10 vs 0 in males and females); and (iv) minimal to slight bronchiole-alveolar hyperplasia (8 vs 0 in males [only minimal]; 9 vs 0 in females). Additionally, one female had a few macrophage aggregates in the bronchus-associated lymphoid tissue. No adverse, treatment-related finding was noted at 0.001 or 0.005 mg/L.

**The LOAEL in male Wistar rats was 0.050 mg/L based on minimal multifocal bronchiole-alveolar hyperplasia in the lung, and 0.050 mg/L in females based on multiple microscopic findings in the lung and associated lymph nodes. The NOAEL was 0.005 mg/L in males and 0.005 mg/L in females.**

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

## A.4.2 Prenatal Developmental Toxicity

### 870.3700a Prenatal Developmental Toxicity Study - Rat

In a developmental toxicity study (MRID No. 00084024), pregnant (CD Charles River) rats (25/dose group) received gavage administration of dicamba (85.3%) in corn oil at dose levels of 0, 64, 160, or 400 mg/kg/day during gestation days 6 through 19. Maternal toxicity limited to the high dose (400 mg/kg/day) was characterized by mortality in three gravid and one non-gravid dams that exhibited neurotoxic signs prior to death; clinical signs of nervous system toxicity that included ataxia, salivation, stiffening of the body when held, and decreased motor activity; statistically significant ($p<0.05$) decreases in body weight gain during the dosing period; and concomitant decreases in food consumption. Dicamba had no effect on any of the cesarean parameters.

**For maternal toxicity, the NOAEL was 160 mg/kg/day and the LOAEL was 400 mg/kg/day based on mortality, clinical signs, body weight changes and decreases in food consumption.** No Treatment-related fetal gross external, skeletal or visceral anomalies (malformations or variations) were seen at any dose level.

**For developmental toxicity, the NOAEL was >400 mg/kg/day; a LOAEL was not established.**

This study is classified **acceptable/guideline** (OPPTS 870.3700a) and satisfies the requirements for a developmental toxicity study in the rat.

### 870.3700b Prenatal Developmental Toxicity Study - Rabbit

In a developmental toxicity study (MRID No. 42429401), inseminated New Zealand White rabbit (19-20/dose) were given oral capsules containing dicamba (90.5%) at dose levels of 0, 30, 150, or 300 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 30 mg/kg/day. At 150 mg/kg/day, maternal toxicity was characterized by abortion (5%) at day 22 and clinical signs such as ataxia, rales, decreased motor activity. At 300 mg/kg/day maternal toxicity was manifested by abortions (20%), clinical signs, decreased body weight and body weight gain and food consumption. Developmental toxicity at 300 mg/kg/day was manifested by irregular ossification of the nasal bones of the skull. At 150 mg/kg/day, increased incidence of abortion was observed and was considered developmental toxicity. In a range-finding study, NZW rabbits were dosed at 0, 62.5, 125, 250, or 500 mg/kg/day from days 6 through 18 of gestation. No maternal or developmental toxicity was observed at 62.5 mg/kg/day. Treatment-related maternal toxicity was manifested by mortality, increased resorptions and reduction in the litter size at 500 mg/kg/day. Clinical signs occurred at 125, 250, and 500 mg/kg/day. Cesarean sections revealed no treatment-related differences between treated and control groups, and no external malformation or variations were seen in any of the fetuses of the treated does.

**The NOAEL for maternal toxicity was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidences of abortion and clinical signs (i.e., decreased motor activity, ataxia). For developmental toxicity, the NOAEL was 62.5 mg/kg/day and the LOAEL was 150 mg/kg/day based on increased incidence of abortion.**

This study is classified **acceptable/guideline** (OPPTS 870.3700b; OECD 414) and satisfies the requirements for a developmental toxicity study in the rabbit.

## A.4.3 Reproductive Toxicity

### 870.3800 Reproduction and Fertility Effects - Rat

In a two-generation reproduction study (MRID 43137101), Sprague-Dawley rats (32 or 28/group) received dicamba technical (86.5%) in the diet at dose levels of 0, 500, 1500, or 5000 ppm (0, 40, 122, or 419 mg/kg/day for males and 0, 45, 136 or 450 mg/kg/day for females, respectively) for two generations. Systemic toxicity was observed at 5000 ppm, manifested as clinical signs in dams from both generations during lactation (tense/stiff body tone and slow righting reflex) and significantly increased relative liver to body weights (112% of control) in both generations and sexes, adults as well as weanlings. The increase (107%) in relative kidney weights observed at 1500 and/or 5000 ppm were not considered to be toxicologically significant due to lack of corroborative gross or histopathological lesions in the kidneys. Sexual maturation among male pups in the F1 generation was significantly delayed at 5000 ppm. Similar effects were not seen in females.

Significantly decreased pup body weights were observed in all generations and matings at 1500 ppm (86 - 90% of control) and at 5000 ppm (74 - 94% of control) throughout lactation, relative to the concurrent controls. There was no adverse effect on pup body weights during the F1 generation lactation period or post-weaning phase at the low and mid doses. However, the PND21 pup body weights for the 1500 ppm group (i.e. 136 mg/kg/day) were within the MARTA (Middle Atlantic Reproduction and Teratology Association, 1993) database historical control range and above the historical control mean value. The study concurrent control groups were also within the historical control range (37.3-65.1 grams). However, both the 2A and 2B generation concurrent control groups PND 21 pup body weights were over 2 standard deviations above the historical control mean value (i.e. 64.95, 61.76 versus 49.33 grams, respectively), thus the MARTA historical control results were utilized for toxicology decisions. As compared to the MARTA historical control database, there were only adverse decreases in pup body weight with statistical significance at 5000 ppm for the F1 generation at both PND 0 (-7.3%) and PND 21 (-7.9%) and the F2B generation at PND 21 (-12.4%).

The F1 animals chosen to produce the F2A and F2B generation offspring were not selected randomly, but rather the male and female animals with the median body weights in each litter were chosen, adding some bias to the F2 phase of the study.

**For parental systemic toxicity, the NOAEL was 122 and 136 mg/kg/day for males and females, respectively, and the LOAEL was 419 and 450 mg/kg/day in males and females based on clinical signs of neurotoxicity. For reproductive toxicity, the NOAEL was 122 mg/kg/day and the LOAEL was 419 mg/kg/day based on delayed sexual maturation in $F_1$ males. For offspring toxicity, the NOAEL was 136 mg/kg/day and the LOAEL was 450 mg/kg/day based on decreased pup body weight during the F1 and F2B generations during lactation.**

This study is classified as **acceptable/guideline** and satisfies the guideline requirements (OPPTS 870.3800; OECD 416) for a two-generation reproduction study in the rat.

## A.4.4 Chronic Toxicity

### 870.4100a (870.4300) Chronic Toxicity – Rat

See 870.4200a

### 870.4100b Chronic Toxicity - Dog

In a chronic oral toxicity study (MRID 40321102), dicamba (86.8, a.i., lot # 52625110) was administered to beagle dogs (4/sex/group) in diet at dose levels of 0, 100, 500, or 2500 ppm (0, 2, 11, or 52 mg/kg/day, respectively) for one year.

The investigated parameters in this study, which included behavior, mortality, body weight, food consumption, hematology, serum chemistry, urinalysis as well as macroscopic and histologic examination of tissues, did not reveal any apparent adverse effect from the test compound. **Therefore, the NOAEL for dicamba was 2500 ppm in the diet (about 52 mg/kg/day), the highest dosage administered in this test. A study LOAEL was not observed. The absence of any adverse effects among treated animals indicated that the MTD was not attained.** This one-year dog study is classified **Acceptable/Guideline** and satisfies the guideline requirement for a chronic toxicity study in dogs.

## A.4.5 Carcinogenicity

### 870.4200a Carcinogenicity Study - Rat

In a combined chronic toxicity/carcinogenicity study (MRID 00146150), groups of 60 male and 60 female CD rats were fed diets containing dicamba (86.8% a.i.; Lot no. 52625110) at 0, 50, 250 ro 2500 ppm for 115 (males) or 117 (females) weeks. These doses correspond to 0, 2, 11 or 107 mg/kg bw/day for males and 0, 3, 13 or 127 mg/kg bw/day for females. Treatment had no adverse effect on survival, body weight, body weight gain, food consumption, hematology, clinical chemistry, urinalysis, organ weights or gross pathology. Histopathology revealed increases in malignant lymphomas in males (0/60, 0/60, 4/60 and 4/60 at 0, 50, 250 and 2500 ppm, respectively) and thyroid parafollicular cell carcinomas in males (1/60, 0/60, 2/60 and 5/60 at 0, 50, 250 and 2500 ppm, respectively). The Cochran-Armitage trend test showed a statistically significant ($p \leq 0.05$) tendency for the proportion of animals with tumors to increase steadily with increase in dose. Pairwise comparison (Fisher's Exact test) showed no statistical significance. Therefore, these tumors were not considered to be toxicologically significant.

Under the conditions of this study, dicamba was not carcinogenic in male or female rats at the doses tested. The lack of systemic toxicity indicate that the animals may have tolerated higher doses (i.e., an MTD was not achieved). However, the doses employed in this study were approved by the Agency (Memo: S. April to R. Taylor, RD, dated 09/26/86).

The administration of dicamba to rats up to 2500 ppm (107 mg/kg/day for males, 127 mg/kg/day for females) in the diet revealed increases in malignant lymphomas in males (0/60, 0/60, 4/60

and 4/60 at 0, 50, 250 and 2500 ppm, respectively) and thyroid parafollicular cell carcinomas in males (1/60, 0/60, 2/60 and 5/60 at 0, 50, 250 and 2500 ppm, respectively). The Cochran-Armitage trend test showed a statistically significant ($p \leq 0.05$) tendency for the proportion of animals with tumors to increase steadily with increase in dose. Pairwise comparison (Fisher's Exact test) showed no statistical significance. Therefore, these tumors were not considered to be toxicologically significant.

The Dose Adequacy Review Team (DART) reviewed the dosages of the study and concluded that the dose levels in the chronic toxicity/carcinogenicity study in rats could have been higher based on kinetics data which indicated that saturation of excretion occurred at a dose ranging from >200 to 400 mg/kg/day. However, retesting at a dose greater than 300 mg/kg/day, for example, would not be recommended based on the saturation data, which showed evidence of saturation of excretion at >200 mg/kg/day. Retesting at a dose of 300 mg/kg/day would not be expected to alter the conclusion that there was no carcinogenic effect. Since the doses in the rat carcinogenicity study (107/127 mg/kg/day) were within a factor of around two fold of the saturation point (>200-400 mg/kg/day), the doses were considered to be adequate for assessment of carcinogenicity. Therefore, the DART concluded that a new chronic toxicity/carcinogenicity study in the rat was not required (TXR No. 0053647).

**870.4200b Carcinogenicity (feeding) - Mouse**

In a carcinogenicity study (MRID 40872401), groups of 52 male and 52 female CD-1 mice were fed diets containing dicamba (86.8% a.i.; Lot no. 52625110) at 0, 50, 150, 1000 or 3000 ppm for 89 (males) or 104 (females) weeks. These doses correspond to 0, 5.5, 17.2, 108 or 358 mg/kg bw/day for males and 0, 5.8, 18.8, 121 or 354 mg/kg bw/day for females. Mortality was significantly increased in males at 150 ppm and at 3000 ppm; the cause of mortality was amyloidosis. The incidence of this lesion was higher than any other single factor among males that died in all groups especially the high dose. Except for a significant decrease at 150 ppm, survival among treated females was comparable to that of the controls. Body weight gain was higher in treated males than control males while there was a 17% decrease in body weight gain in females at 3000 ppm. No treatment-related effects were seen in food consumption, hematology, organ weights or gross pathology. Histopathology revealed a statistically significant ($p < 0.05$) increase in lymphosarcomas in females at 150 ppm only (8/52, 15%) compared to controls (2/52, 4%). The increase was not considered to be treatment-related due to lack of a dose-response and the incidences were within the historical control range (6-33%). Additionally, the incidence in the concurrent control (4%) was below the historical range.

Under the conditions of this study, dicamba was not carcinogenic in male or female mice at the doses tested. The lack of systemic toxicity indicate that the animals may have tolerated higher doses (i.e. and MTD was not achieved). However, the doses employed in this study were approved by the Agency (Memo: S. April to R. Taylor, RD, dated 11/15/84).

The administration of dicamba to mice up to 3000 ppm (358 mg/kg/day for males, 354 mg/kg/day for females) in the diet revealed a statistically significant ($p < 0.05$) increase in lymphosarcomas in females at 150 ppm only (8/52, 15%) compared to controls (2/52, 4%). The increase was not considered to be treatment-related due to lack of a dose-response and the

incidences were within the historical control range (6-33%). Additionally, the incidence in the concurrent control (4%) was below the historical range.

The DART revisited the 1995 decision by the RfD/Peer Review Committee that the mouse carcinogenicity study was not tested at a high enough doses to evaluate carcinogenicity in the mouse. The DART concluded that 3000 ppm is an adequate dose in the mouse cancer study and decided that a new mouse carcinogenicity study was not needed (TXR No. 0053647).

### A.4.6 Mutagenicity

For mutagenicity results, refer to Appendix A.2.

### A.4.7 Neurotoxicity

#### 870.6100 Delayed Neurotoxicity Study - Hen

NA

#### 870.6200 Acute Neurotoxicity Screening Battery

In an acute neurotoxicity study (MRID 42774104) groups of Crl:CD BR rats (10/sex/dose) received a single oral (gavage) administration of dicamba (86.9%) in corn oil at doses of 0, 300, 600, or 1200 mg/kg. Vehicle controls received corn oil only. Positive controls received acrylamide at 50 mg/kg/day by intraperitoneal injection on seven consecutive days. At 300 mg/kg, transiently impaired respiration; rigidity upon handling, prodding or dropping; freezing of movement when touched; decreased arousal and fewer rears/minute compared to controls; impairment of gait and righting reflex were observed in both sexes. In addition, males showed decreased forelimb grip strength. With the exception of the decrease in forelimb grip strength, which persisted until day seven, these effects were observed only on the day of dosing. In addition, at 600 mg/kg, both sexes showed decreases in locomotor activity and males showed significant decreases in tail flick reflex and a raised posture when placed in an open field. These effects were also observed only on the day of dosing. At the highest dose level tested (1200 mg/kg), both males and females showed an impaired startle response to an auditory stimulus. The effect was significant in males on day seven and in females on the day of dosing. In addition, males showed decreases in body weight (5 - 9%), body weight gain (24%) and food consumption (13% between days 0 and 7).
**The LOAEL was 300 mg/kg based on the several neurologic signs listed above; a NOAEL was not established.**

The submitted study is classified as **acceptable/guideline** and satisfies the Guideline requirements (870.6200a) for an acute neurotoxicity study in rats.

#### 870.6200 Sub-chronic Neurotoxicity Screening Battery

In a subchronic neurotoxicity study (MRID No. 43245210), Sprague-Dawley rats (10/sex/dose) were fed diets containing dicamba (86.9%) at 0, 3000, 6000, or 12000 ppm (0, 197.1, 401.4,

767.9 mg/kg/day for males and 0, 253.4, 472.0 or 1028.9 mg/kg/day for females, respectively) for 13 weeks. Neurobehavioral evaluations, consisting of FOB, locomotor activity, and auditory startle response, were conducted at pre-study and during Weeks 4, 8 and 13. No toxicologically significant differences were noted in either the mean body weights or food consumption of the treated animals. Neurobehavioral evaluations at the 4-, 8-, and 13-week evaluations revealed abnormal FOB observations consisting of rigid body tone, slightly impaired righting reflex and impaired gait. At Week 13 the incidences of these findings were decreased. Rigid body tone was also noted during evaluation of the righting reflex and landing foot splay.
**The NOAEL was 401 mg/kg/day and the LOAEL was 768 mg/kg/day based on rigid body tone, slightly impaired righting reflex and impaired gait.** The study is classified as **acceptable/guideline** and satisfies the guideline requirements (870.6200b) for a subchronic neurotoxicity study in the rat.

In a 90-day oral toxicity/neurotoxicity study in Sprague-Dawley (Crl:CD® [SD] rats (MRID 48358001), groups of 16 rats/sex were dosed with MON 11900 in daily diets with either 0, 500, 3000, 6000, or 12000 ppm test material, which corresponded to 0, 34, 197, 397, 803 mg/kg/day in males and 0, 39, 230, 458, 938 mg/kg/day in females. There were 6 animals /sex dose in subset A and B and 4/sex/dose in subset C. Subsets A and B were used for the functional observational battery (FOB) and subsets B and C were used for clinical and pathology determinations.
There were small body weight changes only in males. At the end of the study, 12000 ppm males weighed 5% less than controls with a cumulative weight gain of 9% less than controls; neither value was statistically significant.
Other than one death in a control male; all animals survived to sacrifice. Clinical observations in 12000 ppm males included unkempt appearance (2/16 males, vs 0/16 controls) and gasping/rales (1/16 males, 4 occurrences, vs 0/16 controls). Uncoordinated righting ability was noted in 3/12 males in the 12000 ppm group. There was also lower hindlimb footsplay in 12000 ppm males during week 7. Females in the 12000 ppm group had rigid muscle tone (6/16 females) and one of these showed an impaired equilibrium on 2 different times. Motor activity was unaffected by treatment.
**The NOAEL for MON 11900 is 397 mg/kg/day and the LOAEL is 803 mg/kg/day based on FOB and clinical observations (rigid muscle tone, impaired equilibrium, uncoordinated righting ability, and decreased lower hindlimb foot splay).**

This study is classified as acceptable/guideline and satisfies the guideline requirements for a 90-day rat toxicity study and neurotoxicity study (OECD 408 and EPA OPPTS 870.3100/870.6200).

#### 870.6300 Developmental Neurotoxicity Study

NA

### A.4.8 Metabolism

#### 870.7485 Metabolism - Rat

In a plasma kinetics study, (MRID 44609801), [phenyl-U-$^{14}$C]- dicamba ( [$^{14}$C]-dicamba; 86.0% a.i. radiochemical purity), was administered as a dietary admix to 4 male and 4 female Wistar and Sprague-Dawley at 900, 1500, 3000, 4500, and 12000 ppm (Wistar rats) and 900, 1500,

3000, 6000 and 9000 ppm (Sprague-Dawley rats) for fourteen days, followed by a radioactive dose of 90, 150, 300, 450 mg/kg bw (Wistar rats) and 75, 125, 250, 500 and 800 mg/kg bw by a single gavage dose (in 10 ml/kg body weight 0.5% Tylose CB 30.000 in aqua bidest). Plasma levels were measured at various time intervals following radioactive dose.
A preliminary study in Wistar rats suggests excessive toxicity following repeated gavage doses. Therefore, the main study in both strains of rats was conducted as a dietary ad mix followed by a gavage dose of radiolabeled dicamba. In both strains of rats, the plasma levels reached a maximum level after 0.5-1 hour following the gavage dose and declined thereafter. The $AUC_{0-\infty}$ values were calculated from the plasma concentrations versus time curves at the respective dose levels indicated linear relationship with increase in dose up to a certain dose levels in both strains of rats indicating saturation of excretion. Initial plasma half-life was increased with increasing dose, but terminal half-life remains more or less constant in both strains of rats indicating saturation of excretion. Plasma half-life was increased with increasing dose giving no indication of saturation of oral absorption.
In Wistar rats, the increase in plasma AUC was linear with dose up to a level of 150 mg/kg bw in males and 300 mg/kg bw in females. Above these dose levels, plasma AUC-values increased more than dose. Sprague-Dawley rats showed similar results, with the increase in AUC being linear with dose up to a level of 125 and 250 mg/kg bw in males and females, respectively. Above these dose levels, plasma AUC-values increased more than dose. Considering that oral absorption was not saturated and that initial plasma levels went up with dose, the disproportionate increase in plasma AUC is clearly due to saturation of renal excretion of dicamba resulting in a longer plasma half-life. This is supported by half-life data in both species which showed an increase in plasma half-life with dose. This plasma kinetics study in the rats is classified **Acceptable/Non-guideline (§85-1).**

In a plasma pharmacokinetic study (MRID 46022302), five groups of 4 male and 4 female Wistar rats received diets containing the equivalent of 50, 100, 200, 400, or 800 mg/kg dicamba/day for 90 days (Lot No. 52103810, 87.2% a.i.) . On study days 29, 63, and 91, dietary supplementation of dicamba was stopped and rats in each group received an equivalent gavage dose of $^{14}$C-dicamba (Lot No. 787-0102, >99% a.i., universally labeled in the phenyl group). Blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after treatment and the plasma radioactivity determined.
Absorption of the radiolabeled test material was rapid, with peak plasma concentrations found within 2 hours of treatment. Absorption was not saturated, even at the highest dose, as indicated by increasing plasma concentrations with dose. However, the increase in plasma concentration was disproportionate from dose as shown by the ≥ 2-fold increase in AUC from one dose group to the next at doses >100 mg/kg. Elimination of radiolabel from the plasma was tri-phasic, with the terminal-phase consistent between doses. However, the initial elimination phase increased with dose, particularly in the 400 and 800 mg/kg dose groups and is consistent with excretion saturation. No significant treatment-related differences between the sexes or time of radiolabel administration were found.
This plasma pharmacokinetic study in the rat is classified **Acceptable/Non-guideline** and satisfies its intent.

In a pharmacokinetic study (MRID 46022303), two groups of 3 male Wistar rats were given a single 200 mg/kg gavage dose of $^{14}$C-dicamba (Lot No. 787-0102, >99% a.i., universally labeled

in the phenyl group). One group of rats was pretreated with a 150 mg/kg IP dose of probenecid, a known competitive inhibitor of renal anion transport, 30 minutes prior to dicamba dosing. Blood samples were drawn 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 hours after gavage treatment and the plasma radioactivity determined. The time to peak plasma concentration in rats treated with $^{14}C$-dicamba occurred within 0.5 hours while peak plasma concentration was reached at 1.0 hour in the probenecid/dicamba rats. However, pretreatment with probenecid increased plasma AUC by a factor of 1.54. Although the terminal phase of elimination remained relatively the same, the initial and intermediate elimination phases were increased by a factor of two. These data suggest that both dicamba and probenecid, act as inhibitors of renal anion transport.
This pharmacokinetic study in the rat (MRID 46022303) is classified **Acceptable/Non-guideline** and satisfies its intent.

**870.7600 Dermal Absorption - Rat**

**NA**

## A.4.9 Immunotoxicity

**870.7800 Immunotoxicity**

In an immunotoxicity study (MRID 48081601), BAS 183 H (Dicamba technical) (92.9% a.i., Lot No. COD 001266) was administered to 8 male Crl:WI (Han) Wistar rats/dose in the diet at dose levels of 0, 500, 1500, or 4000 ppm (equivalent to 0, 37, 108, or 307 mg/kg/day) for 28 days. The male rat has been determined as the appropriate species/sex for this study. Cyclophosphamide monohydrate in water was administered daily by gavage to the positive control group (8 male rats) at a rate of 4.5 mg/kg/day. On Day 23, animals were immunized with an intraperitoneal injection of 0.5 mL sheep red blood cells (SRBCs) in 0.9% saline ($4 \times 10^8$ SRBCs)/mL). On Day 29, all animals were sacrificed and T-cell dependent antibody responses (TDAR) were evaluated with an enzyme-linked immunosorbent assay (ELISA).

There were no treatment-related effects on clinical signs, mean body weight, mean body weight gain, or mean food and water consumption. In the positive control group, mean body weights were lower than the control value from Day 3 through Day 28, the differences reaching statistical significance ($p<=0.05$) when measured on Days 24 and 28. Body weight gain in the positive control group also was consistently lower than the control group throughout the study, and was statistically significant over most of the measured intervals ($p<=0.05$) within the study, and over the entire study (i.e., Day 0-28, $p<=0.01$). Additionally, food consumption in the positive control group was lower than the control throughout the study; these data were not statistically analyzed. The decreases in weight, weight gain, and food consumption in the positive control group were considered to be treatment (cyclophosphamide)-related. No unscheduled mortalities occurred in any study group. The NOAEL for systemic toxicity related to treatment with BAS H 183 (dicamba techn.) is 4000 ppm (307 mg/kg/day), the highest dose tested. A LOAEL was not established.

There were no treatment-related changes in anti-SRBC IgM titers as measured by ELISA assay. The mean absolute and relative thymus weights did not differ significantly from the control in any test substance treatment group. In the positive control group, mean anti-SRBC IgM titers

were markedly lower than the control, and absolute and relative spleen and thymus weights were significantly reduced when compared with the control (p<=0.01).

The Natural Killer (NK) cell activity was not evaluated. Evaluation of toxicity database of dicamba including subchronic, chronic toxicity and reproduction studies showed no treatment-related effects on spleen and thymus weights and histopathology parameters that would suggest the potential for immunotoxicity. Under the HED guidance, if the TDAR assay is negative and evaluation of observational endpoints from all available toxicology database provide no evidence of immunotoxicity, the test article is considered negative for immunotoxicity and evaluation of NK cells activity is not necessary.

**Under conditions of this study, the NOAEL for immunotoxicity in male rats is 4000 ppm (307 mg/kg/day), the highest dose tested. A LOAEL was not established.**

This 4-week dietary immunotoxicity study in the rat is **acceptable/guideline** and satisfies the guideline requirement for an immunotoxicity study (OPPTS 870.7800).

### A.4.9 Special Studies: Toxicity of Dicamba Metabolites or Amine Salts

#### 870.3100 DCGA 28-Day Oral Study in Rats

In a 28 day dietary toxicity test (MRID 47899506) groups of 10 rats/sex/group were exposed to DCGA (MON 52724) (Purity 98.1% Lot/batch No GLP-0904-19809-T) at dietary concentrations of 0, 500, 3000, 6000,or 12000 ppm. The average test substance consumption over the entire study was 0, 40, 240, 474, and 956 mg/kg/day for males and 0, 45, 265, 519, and 1063 mg/kg/day for females. All animals were observed twice daily for moribundity and mortality, clinical examinations were performed daily, and individual body weights were recorded weekly. Food consumption, functional observational battery (FOB) and motor activity were recorded twice weekly.
All animals survived to the scheduled necropsy. There were no adverse test substance related clinical observations, effects on organ weights or histological, or macroscopic findings. FOB and and motor activity were unaffected by treatment. Body weights were decreased 9% in males and 6% in females (not statistically significant).
**The NOAEL was 474 mg/kg/day and the LOAEL was 956 mg/kg/day based upon decreased body weight in males.**

This study is classified as acceptable/guideline, and it satisfies the guideline requirement for a 28-day oral toxicity study in rodents (OECD 407, OPPTS 870.3050).

#### 870.3100 DCSA 90-Day Oral Study in Rats

In a 90 day dietary study (MRID 47899507), Sprague-Dawley (Crl:CD®[SD]) (10 rats/ sex/group) were exposed to MON 52708 ( purity 97.9%; Lot/batchGLP-0603-16958-T) for 90-days. Final dietary concentrations were 500, 3000, 6000 and 12000 ppm. Due to potential problems with palatability observed in a previous range finding study, rats in the higher dose groups received slowly increasing doses during the first 1 to 2 weeks. Group 4 rats received the

3000 ppm diet during week 0 and the 6000 ppm diet during weeks 1 through 12. Group 5 rats received the 3000 ppm diet during week 0, the 6000 ppm diet during week 1 and the 12000 ppm diet during weeks 2 through 12.) The control group (Group 1) received the basal diet only throughout the study. The average test substance consumption over the entire study was 0, 32, 195, 362, or 659 mg/kg/day for males and 0, 37, 222, 436, or 719 mg/kg/day for females.

All animals were observed twice daily for mortality and morbidity. Clinical observations were made daily and detailed physical exams conducted weekly. Body weights and food consumption were measured weekly. Functional observational battery (FOB), locomotor activity and ophthalmic examination data were recorded prior to beginning exposure to MON 52708 and at the end of the study (week 12). Hematology, serum chemistry and urinalysis assessments were conducted during study week 13. Complete necropsies were conducted on all animals at study week 13. Selected organs were weighed at necropsy and selected tissues from all animals were examined microscopically.

Lower body weights were noted in the 12000 ppm group males and females throughout the study after dose ramping was concluded and final dosing levels were achieved (end of study week 2). Terminal mean body weights for the 12000 ppm males and females were 28.1% and 29.7% lower than controls, respectively. Body weights and food consumption in the 6000 ppm group females were also statistically significantly lower compared to controls during the first few weeks of the study after ramping was concluded and generally remained lower but were not statistically significantly different for the rest of the study.

Food consumption in 12000 ppm males and females was decreased from the end of week 2 until approximately midway through the study. After approximately week 7, food consumption was increased in 12000 ppm males compared to controls and in 12000 ppm females was comparable to controls.

In the functional observation battery, there were no treatment-related effects noted during home cage, handling, open field, sensory, neuromuscular, or physiological observations. For the motor activity assessment, ambulatory counts were increased in 12000 ppm males by 59% ($p<0.005$), compared to controls, during the first 15 minute interval. Ambulatory counts were increased for that group in 2 other intervals, but not with statistical significance.

Hematological effects were noted in the 12000 ppm group. Effects included decreased red blood cell count, haemoglobin, MCHC, and hematocrit, and were more pronounced in females than in males.

Liver enzymes, including alkaline phosphatase, aspartate aminotransferase, and alanine aminotransferase, were increased in the 12000 ppm group. Relative liver weights were higher in the 12000 ppm group compared to controls, but absolute liver weights were not statistically different. There were no microscopic findings in the liver.

Microscopic lesions included an increase of bone marrow depletion in the sternum of the 12000 ppm group males and 6000 and 12000 ppm group females and hyperplasia of the epithelium in the glandular stomach of 12000 ppm group males and females. There were also four erosions in the glandular stomach, one each in males from the 6000 and 12000 ppm groups and two in females from the 12000 ppm group.

**The NOAEL is 362 mg/kg/day and the LOAEL is 659 mg/kg/day based on decreased body weight, increased motor activity, decreased hematological parameters, and increased liver enzymes.**

This study is classified as acceptable/guideline and satisfies the guideline requirement for a 90-day feeding study in the rat (EPA OPPTS guideline 870.3100 and OCED guideline Section 408).

### 870.3100 Dicamba BAPMA 90-Day Oral Study in Rats

In a 90-day oral toxicity study (MRID 49441801), Dicamba BAPMA Salt (69.5% a.i. Dicamba acid; batch#: 1781-6) was administered to 10 Wistar rats/sex/dose in the diet at dose levels of 0, 4317, 8633, or 17266 ppm (equivalent to 0, 257, 513, and 1027 mg/kg bw/day in males and 0, 294, 589, and 1178 mg/kg bw/day in females). The test diets were equivalent to 0, 3000, 6000, and 12000 ppm Dicamba acid (equivalent to 0, 178, 357, and 714 mg/kg bw/day in males and 0, 205, 409, and 819 mg/kg bw/day in females). Evaluated parameters included mortality, clinical signs, body weight, food consumption, ophthalmological examinations, functional observational battery (FOB), clinical pathology, organ weight, and gross and histopathological examination.

There were no treatment-related effects on mortality, clinical signs, FOB, body weights, food consumption, ophthalmoscopy, urine parameters, macroscopic findings, or histopathology. Treatment-related increased absolute and relative kidney weights were noted in males of the high-dose study group (absolute weight 15% greater than controls [n.s.] and relative weight 20% greater than controls). Total bilibrubin levels were significantly decreased 41-79% in all treated animals, and the changes were considered related to treatment, but were not considered adverse. In males of the high-dose group, prolonged prothrombin time (9.5%) and increased incidence of urine triple phosphate crystals were observed. In females, creatinine levels were significantly increased 33% at the high-dose. In both sexes at the high-dose, total protein and globulin levels were significantly decreased 5-16%. **Therefore, under the conditions of this study, the LOAEL of Dicamba BAPMA Salt is 17266 ppm (1027 mg/kg bw/day in males and 1178 mg/kg/day in females; corresponding to 714 and 819 mg/kg bw/day Dicamba Acid in males and females, respectively), based on kidney effects and altered hematology (increased prothrombin time in males) and clinical chemistry (increased creatinine levels in females and decreased total protein and globulin levels in both sexes) parameters. The NOAEL is 8633 ppm (513 mg/kg bw/day in males and 589 mg/kg/day in females; corresponding to 357 and 409 mg/kg bw/day Dicamba Acid in males and females, respectively).**

This 90-day oral toxicity study in the rat is **Acceptable / Guideline** and satisfies the guideline requirement for a 90-day oral toxicity study (OCSPP 870.3100; OECD 408).

### 870.3150 DCSA 90-Day Oral Study in Dogs

In a 90 day oral capsule study (MRID 48358002), Beagle dogs (5 animals/sex/group) were treated with MON 52708 (purity 97.7%; Lot/batchGLP-0603-16958-T) for 90 days with doses of 0, 15, 50 and 150 mg/kg/day.

All animals were observed twice daily for mortality and morbidity. Clinical observations were performed daily and detailed physical exams were conducted weekly. Body weights were measured weekly. Food consumption was recorded daily and reported weekly. Clinical pathology evaluations included hematology, coagulation, serum chemistry and urinalysis and

were conducted prior to initiation of dosing and during study weeks 6 and 13. Ophthalmic examinations were conducted prior to initiation of dosing and during study week 12. Complete necropsies were conducted on all animals during study week 13. Selected organs were weighed at necropsy and selected tissues were examined microscopically.
One female in the 150 mg/kg/day dose group was euthanized in extremis on day 50 of the study. Death was associated with repeated emesis, electrolyte imbalance, and severe dehydration. All other animals survived to the scheduled necropsy.

Statistically significant decreases were observed in cumulative body weight gains in both males and females in the 150 mg/kg/day groups. Absolute mean body weights in these groups were about 11% lower than controls at the end of the study, though the differences were not statistically significant. Decreased food consumption was observed in females in the 150 mg/kg/day group during study weeks 1 -2 and 3-4. Male food consumption was not different from controls. Abnormal excreta and emesis were present in the 150 mg/kg/day male and female groups. Abnormal excreta began on study day 0; emesis began on study day 2. Both effects persisted to the end of the study.
Coagulation effects were observed in both males and females: APTT values were higher in males in the 150 mg/kg/day at study week 13 and in females in the 150 mg/kg/day group at study week 6.
Liver weights relative to body weights were higher in males and females in the 150 mg/kg/day groups. Hypertrophy of periportal hepatocytes was observed in the livers of both sexes in the 150 mg/kg/day groups.

**The NOAEL is 50 mg/kg/day and the LOAEL is 150 mg/kg/day based on mortality, decreased body weight, clinical signs (abnormal excreta and emesis), and increased clotting time.**

This study is classified as acceptable/guideline and satisfies the guideline requirement (EPA OPPTS guideline 870.3150 and OCED guideline Section 409) for a 90-day dog study.

### 870.3200 Dicamba DGA 21-Day Dermal Study in Rabbits

In a 21-day dermal toxicity study (MRID No. 43554206) New Zealand White rabbits [5/sex/dose] were given repeated dermal applications of the diglycolamine (DGA) salt (59%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for a total of 15 applications during a 3 week period. No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. **A NOAEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOAEL was not established for either end-point.**

This study is classified as Core Guideline and satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

### 870.3200 Dicamba IPA 21-Day Dermal Study in Rabbits

In a 21-day dermal toxicity study (MRID No. 43554207) New Zealand White rabbits [5/sex/dose] were given repeated dermal applications of the isopropylamine (IPA) salt (41%) of dicamba at 0, 100, 500 or 1000 mg/kg, 6 hours/day, 5 days/week for a total of 15 applications during a 3 week period. No treatment-related dermal reactions or histopathological dermal lesions were seen. No systemic toxicity was seen; treatment had no adverse effect on survival, clinical signs, mean body weights, body weight gains, hematology, clinical chemistry, organ weights or gross and histopathology. **A NOAEL of 1000 mg/kg/day (Limit-Dose) was established for both dermal irritation and systemic toxicity. A LOAEL was not established for either end-point.**

This study is classified as **Core Guideline** and satisfies the data requirement [§82-2] for a 21-day dermal toxicity study in rabbits and is acceptable for regulatory purposes.

### 870.3465 Dicamba BAPMA 28-Day Inhalation Study in Rats

In a nose-only inhalation toxicity study (MRID 49441803), four groups of Crl:WI(Han) rats (10/sex/group; ~10 weeks of age) were administered Dicamba BAPMA Salt [84.7%, equivalent to 69.5% Dicamba acid (Batch No. 1781-6)] as a dust aerosol at target exposure concentrations of 0, 0.0014, 0.0072, or 0.036 mg/L (respective actual concentrations of 0, 0.0015, 0.0070, and 0.0352 mg/L) for 28 days.

There were no mortalities or clinical signs observed at any exposure concentration. No substance-related adverse findings were observed on body weight, ophthalmology examinations, food consumption, or clinical pathology parameters in blood. Plasma concentrations of Dicamba acid after 22 days of exposure increased with exposure concentration, but not proportionally to the 5-fold increase in exposure between the mid- and high-exposure concentrations. The respective mean values of female animals were higher than those of the males. Microscopic examination of tissues showed that the test substance was a respiratory tract irritant with adverse effects on the nasal cavity, larynx, trachea, lungs, and the lung-associated lymph nodes. **Nasal cavity**: In Level I, focal degeneration/regeneration of the respiratory and/or transitional epithelium was observed in 1 male and 1 female from the mid exposure group (minimal severity), and in 8 males and 5 females from the high exposure group (minimal to slight). Two males and two females at the high concentration showed minimal focal squamous cell metaplasia of the respiratory epithelium in the septum. In Level II, one female at the high concentration showed an ulcer in the epithelium of the septum. **Larynx**: Ulcers in epithelial tissues were observed in males at incidences of 2/10, 5/10, and 8/10, respectively, in the low-, mid-, and – high-exposure groups. Minimal focal inflammation was observed in Level I or Level II in 3 males at the low concentration, 1 male and 1 female at the mid concentration, and in 1 male and 3 females at the high concentration. Single or multi-focal hyperplasias were observed in Level I and/or Level II in 5 males and 4 females at the low concentration, 8 males and 7 females at the mid concentration, and in 7 males and 7 females at the high concentration. **Trachea**: Minimal or slight focal degeneration/regeneration of the respiratory epithelium was observed in 2 males at the mid concentration, and in 5 males and 1 female at the high concentration. **Lung**: Minimal to slight inflammation was observed in bronchi and/or alveoli in most to all of the males and females at the mid- and high-concentration. Minimal multifocal bronchiolo-alveolar hyperplasia was observed in 2 males at the high concentration and in 1 female at the mid concentration. Minimal hypertrophy of single terminal bronchi was observed in 6 males and 3 females at the

high concentration. The incidence of minimal or slight multifocal alveolar histiocytosis increased in males from all three exposed groups and in females from the mid- and high-concentration groups. The incidence of minimal or slight alveolar macrophage aggregates was increased in males at the mid- and high-concentration and in females from all three exposed groups. Tracheobronchial and mediastinal lymph nodes: Minimal to slight lympho-reticulocellular hyperplasia in one or both of these lymph nodes was observed in males at the mid- and high-exposure concentrations and in females at all three concentrations. Macrophage aggregates were observed in both sexes at the mid- and high-exposure concentrations.

**The LOAEL in Wistar rats was 0.0014 mg/L based on ulcers in epithelial tissues of the larynx and single/multi-focal hyperplasias in the larynx. A NOAEL was not identified.**

This inhalation toxicity study is classified as **Acceptable (Guideline)** and satisfies the guideline requirement for 4-week inhalation toxicity study in rats (OCSPP 870.3465).

### 870.3650 BAPMA Base OECD 422 Developmental-Reproduction Study

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, N,N-Bis(3-aminopropyl)methylamine (99.6% a.i., Batch No. O2903) was administered to 10 Wistar rats/sex/dose by gavage in deionized water at dose levels of 0, 25, 100, or 500 mg/kg bw/day for at least 14 days prior to mating, throughout mating, and up to and including the day prior to sacrifice. Terminal sacrifices took place after 28 days of treatment in males and after 56 days of treatment in females. Evaluated parameters in the parental animals included functional observational battery (FOB), motor activity, hematology, clinical chemistry, urinalysis, organ weights, macroscopic examination, and histopathology

In the high-dose group, there was 100% mortality (both sexes) within the first four days of treatment. One male was found dead on study day 3 and one female was found dead on study day 1. Due to clinical signs including labored respiration, piloerection, unsteady gait, hypothermia, semiclosed eyelids, and abdominal position, all animals of the high-dose group were sacrificed *in extremis* between study days 1 and 4. Treatment-related post mortem findings in these animals included red discoloration and lesions of the gastrointestinal track including extensive areas of erosion and/or ulceration, hemorrhagic inflammation, and blunting and fusion of villi. Tubular necrosis of the kidney was also observed.

No treatment-related mortality or clinical signs were observed in the low- and mid-dose groups. There were no treatment-related effects on mean body weight, food consumption, clinical pathology, or gross and microscopic necropsy findings of the low- and mid-dose groups. Motor activity was decreased by 24% at 100 mg/kg/day. Body weight loss was observed in the mid-dose group (-2.2 g vs. 4.6 g in control) during lactation, but was not considered adverse because it did not affect mean body weights. Water consumption was decreased by 22-47% during premating through GD 14 and was significantly decreased by 19% in females of the mid-dose group at the end of gestation (GD 19-20). In the absence of correlated effects on clinical signs, clinical pathology, organ weights, and/or gross or microscopic findings, the toxicological significance of the decreased water consumption is unclear. **Deaths occurred in the dams at 500 mg/kg bw/day. Therefore, the parental systemic NOAEL is 25 mg/kg bw/day, and the**

**LOAEL is 100 mg/kg/day based on decreased motor activity and water consumption, results from the surviving animals.**

No animals in the high-dose groups were mated due to excessive toxicity and mortality during the premating period. No evidence of reproductive toxicity was found. Maternal treatment did not result in decreased *in utero* or postnatal survival, altered growth, abnormal clinical signs, or an increased incidence of gross abnormalities of the offspring. **Therefore, the reproductive/developmental LOAEL is not identified, and the reproductive/developmental NOAEL is 100 mg/kg bw/day.** However it must be noted that there were only six and seven litters with live fetuses in the low- and mid-dose groups, respectively. Although the low numbers of litters are not treatment-related, they still limit the sensitivity of this study to detect effects on pregnancy, maternal and suckling behavior, and growth and development of the $F_1$ offspring from conception to day 4 post-partum.

This study is **Acceptable/ Non-Guideline** and does satisfies the guideline requirement for a reproductive/developmental toxicity screening study (OCSPP 870.3650; OECD 422) in the rat.

### 870.3700a Dicamba BAPMA Rat Developmental Study in Rats

In a developmental toxicity study (MRID 49441802), Dicamba BAPMA salt [84.7% w/w Dicamba BAPMA; 69.5% w/w Dicamba (acid equivalent), batch# 1781-6] was administered to 25 female Wistar rats/dose in 1% aqueous carboxymethylcellulose suspension by oral gavage at dose levels of 0, 29, 86, or 288 mg/kg bw/day (corresponding to 20, 60, or 200 mg/kg bw/day Dicamba acid) on gestation days (GDs) 6 through 19, inclusive. Body weights and food consumption were monitored regularly until sacrifice on GD 20. Dams were necropsied, and gravid uterine weight, numbers of corpora lutea, and numbers and distribution of live and dead fetuses and early and late resorptions were recorded. Fetuses were sexed, weighed, and investigated for external findings; approximately one-half of the fetuses of each litter were examined for soft tissue findings and the remaining fetuses for skeletal findings (inclusive of cartilage). Individual placental weights also were recorded.

At 86 and 288 mg/kg bw/day, maternal toxicity was characterized by increased incidences of adverse clinical signs, including unsteady gait, convulsions, and ataxia (occurrences/affected animals at 86 mg/kg/day: 114/24, 3/2 and 4/2; at 288 mg/kg/day: 74/20, 187/25 and 63/20, respectively, out of 25 total animals for both groups). Observations in the mid-dose females began after dosing and persisted for a maximum of 3 hours, with the earliest observations recorded on GD 6 (unsteady gait) or GDs 12-13 (convulsions/ataxia), while those in the high-dose females began after dosing, persisted for a maximum of 4 hours, and were first noted on GDs 6-7. Also in the 288 mg/kg/day females, body weight gain and food consumption was significantly reduced compared to controls during intervals at the beginning of treatment, and non-statistically significantly reduced for the overall treatment period as follows: body weight gain: -20% during GDs 6-13, -8% during GDs 6-19; food consumption: -8% during GDs 6-10, -7% during GDs 6-19. The corrected (for gravid uterine weight) body weight gain was significantly lower in the high dose group by 16%, indicating that the decreased weight gain was a maternal effect. No maternal toxicity was apparent at the low dose of 29 mg/kg/day. No

treatment-related effects on maternal cesarean section parameters were noted at any dose level for this study.

**The maternal LOAEL for Dicamba BAPMA salt in rats is 86 mg/kg bw/day (corresponding to 60 mg/kg bw/day Dicamba acid equivalent), based on adverse clinical signs of unsteady gait, ataxia, and convulsions. The maternal NOAEL is 29 mg/kg bw/day (corresponding to 20 mg/kg bw/day Dicamba acid equivalent).**

No developmental toxicity was evident as a result of maternal treatment with up to 288 mg/kg/day of Dicamba BAPMA salt. Fetal weights, fetal sex ratios, post implantation loss and numbers of viable fetuses, implantation sites, resorptions, and corpora lutea in all dose groups were comparable to the control group. The infrequent occurrence and nature of fetal malformations observed in the study were not considered treatment-related, and visceral and skeletal variations were comparable to controls and/or did not exhibit a dose-response relationship.

**The developmental LOAEL for Dicamba BAPMA salt in rats was not determined. The developmental NOAEL is greater than or equal to 288 mg/kg bw/day (200 mg/kg bw/day Dicamba acid equivalent).**

The developmental toxicity study in the rat is classified **Acceptable/Guideline** and satisfies the guideline requirement for a developmental toxicity study (OCSPP 870.3700; OECD 414) in the rat.

### 870.3700a DCSA Rat Developmental Study in Rats

In a prenatal developmental toxicity study (MRID 47899519) groups of 25 bred female Crl:CD (SD) rats were administered MON 52708 (purity 97.9%; Lot/batch# GLP-0603-16958-T) by oral gavage at doses of 0, 10, 30 and 100 mg/kg/day from gestation days 6 through 19. The doses for this study were based on a previous prenatal developmental toxicity dose range-finding study (MRID47899518).

All animals were observed twice daily for mortality and moribundity, and individual clinical observations were recorded from gestation days 0 through 20. Animals were also observed for signs of toxicity approximately 1 hour following dose administration. Body weights and food consumption were recorded on gestation days 0 and 6-20. On gestation day 20, a laparohysterectomy was performed on each female. The uteri, placentae and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Gravid uterine weights were recorded, and net body weights and net body weight changes were calculated. The fetuses were weighed, sexed and examined for external, visceral and skeletal malformations and developmental variations.

All females survived to the scheduled necropsy on gestation day 20; there were no test article-related clinical or macroscopic findings at any dose level. Mean maternal body weights, body weight gains, net body weights, net body weight gains, gravid uterine weights and food consumption in all test article-treated groups were generally similar to those in the control group.

No test article-related effects on intrauterine growth, survival or fetal morphology were observed at any dose level.

Doses in this study were based upon toxicity in a pilot study (MRID47899518, see Appendix). In the pilot study clinical observations at 200 mg/kg/day included salivation, red and/or clear material around the mouth and/or nose, and yellow or brown material around the genital area. Fetal body weights were decreased 14% in the 200 mg/kg/day group compared to controls.

**The maternal and developmental NOAELs are both 100 mg/kg/day, the highest dose tested. A LOAEL was not determined**.

This study is classified **totally reliable (acceptable/guideline) when considered in conjunction with the range-finding study** (MRID47899518) and satisfies the guideline requirements (EPA OPPTS guideline 870.3700 and OCED guideline 414).

**DCSA Range-Finding Study for Rat Developmental Study**

In a prenatal development toxicity range finding test (MRID47899518) groups of 8 bred female Crl:CD(SD) rats were administered by MON 52708 (purity 97.9%; Lot/batch no GLP-0603-16958-T) by oral gavage at doses of 0, 50, 200, 500 or 1000 mg/kg/day from gestation days 6-19. All animals were observed twice daily for mortality and moribundity, and individual detailed clinical observations were recorded from gestation days 0 through 20. Animals were also observed for signs of toxicity at the time of dose administration and approximately 1 hour following dose administration. Body weights and food consumption were recorded on gestation days 0 and 6-20. On gestation day 20, a laparohysterectomy was performed on each surviving female. The fetuses were weighed, sexed and examined for external malformations and developmental variations.

In the 1000 mg/kg/day group, 7 of the females were found dead and 1 female was euthanized in extremis on gestation day 7, 8 or 9. In the 500 mg/kg/day group, 2 females were found dead, 1 each on gestation days 8 and 10. All other females survived to the scheduled necropsy. Clinical findings for surviving females in the 200 and 500 mg/kg/day groups included salivation and red and/or clear material around the mouth and/or nose. In addition, in the 500 mg/kg/day group, excessive pawing and wiping of the mouth on the cage were noted.
Mean maternal body weight losses and/or lower mean body weight gains and lower food consumption, mean gravid uterine weights, net body weights and/or net body weight gains (relative to the control group) were generally noted in the 200 and 500 mg/kg/day groups throughout the treatment period. Body weight gain for the 200 mg/kg/day group was 92 g vs 117 g in controls. Body weights were also reduced in the 500 mg/kg/day, though this was in part due to the 100% resorptions at that dose.

At the scheduled necropsy, no remarkable macroscopic findings were noted in the surviving dams at any dose level. Mean absolute liver weights in the 200 and 500 mg/kg/day groups were 7.0% and 19.0% lower than the control group value, respectively. In addition, slightly higher mean absolute spleen and kidney weights (16.7% and 11.6%, respectively) were noted in the 500 mg/kg/day group when compared to the control group values.

Evaluation of laparohysterectomy parameters in the 1000 mg/kg/day group was precluded by the death of all females in this group. Surviving females in the 500 mg/kg/day group had early resorptions of all litters. In the 200 mg/kg/day group, mean fetal weight was decreased 14% compared to controls. No malformations or developmental variations were noted in any fetuses in the control or test article-treated groups following an external examination.

Because this range finding study was not intended to fulfill a guideline requirement, NOAELs and LOAELs are not assigned. This study is suitable for use in dose selection for a definitive guideline study.

### 870.3700a DCGA Developmental Study in Rats

In a dose range-finding toxicity study (MRID 47899520) four groups of eight bred female Crl:CD(SD) rats per dose group were exposed to MON 52724 (Purity 96.3%; Lot/batch No GLP-0903-19699-T ) by gavage with corn oil at doses of 0, 50, 200, 500, and 1000 mg/kg/day. Animals were observed twice daily for moribundity and mortality and individual detailed clinical observations were recorded from day 0 through gestation day 20. Body weights and food consumption were recorded from gestation days 0 and 6-20. On gestation day 20, a laprohysterectomy was performed on each of the surviving animals and the uteri, placentae, ovaries were examined, and the number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded. Fetuses received an external examination but not a soft tissue or skeletal examination.

Mean body weights were 4.0% to 6.6% lower during gestation days 13-20 in the 500 mg/kg/day group and 4.4% to 12.1% lower during gestation days 12-20 in the 1000 mg/kg/day group. Five of the eight females in the 1000 mg/kg/day group died or were euthanized *in extremis* during gestation days 12-19. Clinical findings in dams included rales and red or clear material on body surfaces at doses of 200 mg/kg/day and above. There were no effects observed on uterine growth, survival, external malformations or variations.

Because this range finding study was not intended to fulfill a guideline requirement, NOAELs and LOAELs are not assigned. This study is suitable for use in dose selection for a definitive guideline study.

### 870.3700b DCSA Developmental Study in Rabbits

In a developmental toxicity study (MRID 47899522), groups of twenty-five mated female New Zealand white rabbits were exposed to DCSA (MON 52708) (Purity 97.7%; Lot/batch No GLP-0603-16958-T ) by gavage from gestation days 6-28 at doses of 0, 10, 25, or 65 mg/kg/day. All animals were observed twice daily for moribundity and mortality and individual detailed clinical observations, body weights, and food consumption were recorded. On gestation day 29, a laprohysterectomy was performed on each surviving females and the uteri, placentae, ovaries were examined, and the number of fetuses, early and late resorptions, total implantations and corpora lutea were recorded.

One control female and one female in the 65 mg/kg/day group died with cause of death undetermined. One female in the 10 mg/kg/day group aborted. All treatment groups had decreased defecation. There were no toxicologically significant test substance related effects observed on survival, clinical signs, body weight, food consumption, intrauterine growth, pup survival, external malformations or morphology of fetuses.

Although no toxicity occurred in this study at the high dose of 65 mg/kg/day, the does could not have tolerated a much higher dose because 100 mg/kg/day was found to be a maternally lethal dose in the range finding study (MRID 47899521).

**The maternal and developmental NOAELs are 65 mg/kg/day, the highest dose tested. The maternal and developmental LOAELs were not determined**.

Therefore, this study is classified **as acceptable/guideline when considered in conjunction with the range finding study** and satisfies the guideline requirements for a developmental toxicity study in rabbits (OPPTS 870.3700, OECD 414).

### 870.3800 DCSA Reproduction Study in Rats

In a dietary two-generation reproductive toxicity study (MRID 47899517) DCSA (MON 52708) (purity 97.7%, Lot/Batch no., GLP-0603-16958-T) was administered continuously in the diet to groups of male and female Crl:CD(SD) rats (30/sex/group) at dose levels of 0, 50, 500 and 5000 ppm. One litter per dam was produced in each generation.

Mean test substance consumption for the F0 males was 4, 37 and 362 mg/kg/day and for F0 females was 4, 43 and 414 mg/kg/day during the premating period, 3, 34 and 323 mg/kg/day during gestation and 8, 78 and 610 mg/kg/day during lactation, for the 50, 500, and 5000 mg/kg/day groups, respectively.
Because all surviving offspring of the F0 animals in the 5000 ppm group were euthanized on PND 21 due to pup mortality and a high incidence of total litter loss among the dams, no offspring of the F0 animals in the 5000 ppm group were selected for the F1 generation. Mean test substance consumption for the F1 males was 4 and 41 mg/kg/day and for F1 females was 5 and 52 mg/kg/day during the premating period, 3 and 34 mg/kg/day during gestation and 8 and 79 mg/kg/day during lactation, for the 50 and 500 mg/kg/day groups, respectively.

Three additional groups of female rats (10/group) were included in this study for evaluation of clinical and histological pathology parameters. These non-mated satellite animals were administered either basal diet or the test substance in the diet for at least 90 consecutive days; dietary concentrations were 0, 50 and 500 ppm. No differences in clinical pathology or histological parameters were observed when comparing control and test substance-treated animal data. Mean test substance consumption for the satellite phase females in the 50 and 500 ppm groups was 4 and 42 mg/kg/day, respectively.

F0 and F1 parental survival was unaffected by test diet administration at all exposure levels. No remarkable clinical findings were noted at any exposure level tested in the F0 or F1 generations. Parental body weight and food consumption parameters were not adversely affected at exposure

levels of 50 and 500 ppm in either generation. At an exposure level of 5000 ppm (evaluated only in the F0 generation), test substance-related reductions in mean body weight gain, food consumption and food efficiency were noted during the first month of test diet exposure, which resulted in lower mean body weights throughout the pre-mating period (females) or entire generation (males). Lower mean food consumption was also noted for the 5000 ppm group females throughout gestation and lactation.

There were no indications of adverse effects on reproductive performance in either the F0 or F1 generations. Male and female mating and fertility indices, male copulation indices, female conception indices, pre-coital intervals, spermatogenic endpoints, lengths of the estrous cycle and gestation, and live litter size were similar in all exposure groups. No test substance-related effects in gross pathology, organ weights or histopathology were noted in F0 or F1 parental animals. Additionally, ovarian follicle counts for the test substance-exposed F0 (5000 ppm, high-dose group) and F1 (500 ppm, high-dose group) females were similar to the control group values.

Test substance-related effects on pre-weaning offspring were noted at an exposure level of 5000 ppm (F1 pups) and included decreased pup survival during PND 0-1, 1-4 (pre-selection), 7-14 and 14-21 (due primarily to 7 females with total litter loss), clinical signs of toxicity (pale body, blackened ventral abdominal area, distended abdomen, uneven hair growth and desquamation) and lower body weights and weight gains during PND 1-21.

As a result of pup mortality and a high incidence of total litter loss among the F0 dams at 5000 ppm, all surviving offspring of the F0 animals in the 5000 ppm group were euthanized on PND 21; therefore, a dosage level of 5000 ppm group was not evaluated in the F1 generation. At 500 ppm, mean $F_1$ male and female pup body weights on postnatal days 14 and 21 were reduced approximately -6% to -9% of controls; female pup body weight was also reduced at week 18 (-7%). Hyperkeratosis was noted upon histological evaluation of the F1 pups in the 5000 ppm group that had gross skin lesions or clinical findings of desquamation or uneven hair loss/hair growth.

No test substance-related effects on offspring survival, general physical condition, body weights, macroscopic pathology and organ weights were noted at exposure levels of 50 ppm for F1 or F2 pups. Mean ages and body weights on the day of attainment of balanopreputial separation and vaginal patency were unaffected by treatment in any group.

**The parental NOAEL is 37 mg/kg/day and the parental LOAEL is 362 mg/kg/day based upon decreased body weight.**

**No reproductive toxicity was noted and the reproductive NOAEL is 362 mg/kg/day; the reproductive LOAEL was not attained.**

**The offspring NOAEL is 4 mg/kg/day and the offspring LOAEL is 37 mg/kg/day based upon decreased pup body weight in $F_1$ pups on postnatal days 14 and 21 (both sexes) and at week 18 (females only).**

This study is classified as acceptable/guideline and satisfies the guideline requirement for a reproduction study (OECD 416, OPPTS 870.3800, PMRA DACO 4.5.1).

### 870.4200a DCSA Chronic Toxicity/Carcinogenicity in the Rat

In this combined chronic toxicity/carcinogenicity study (MRID 47899516, chronic toxicity and MRID 48358003, carcinogenicity), Sprague Dawley (Crl:CD®[SD]) rats were exposed to MON 52708 (purity 97.4% - 97.7%; Lot/batch no GLP-0603-16958-T) in the diet. Dietary concentrations were 0, 10, 100, 300, 1000 or 3000 ppm. Doses for the chronic toxicity phase were 0.6, 5.6, 16.9, 56.9, and 171.2 mg/kg/day for males and 0, 0.7, 6.9, 20.5, 68.2, and 206.2 mg/kg/day for females. Doses for the carcinogenicity phase were 0.5, 5.0, 14.6, 48.8, and 150.1 mg/kg/day in males and 0.6, 6.1, 18.4, 60.9, and 181.5 mg/kg/day in females. There were 50 male and 50 female rats in the 24 month carcinogenicity study and 20 male and 20 female rats in the 12 month chronic toxicity study.

All animals were observed twice daily for mortality and moribundity. Clinical examinations were performed daily, and detailed physical examinations were performed weekly. Individual body weights and food consumption were recorded at least weekly for the first 13 weeks of the study, and at least once every four weeks thereafter. Ophthalmic examinations were performed during study weeks 2 and 51. Clinical pathology parameters were evaluated for the last 10 surviving animals/sex/group: hematology and serum chemistry were evaluated during study weeks 12 and 25, and at the scheduled necropsy (study week 52); coagulation parameters were evaluated only at the scheduled necropsy (study week 52); and urinalysis parameters were analyzed during study week 25 and at the scheduled necropsy (study week 52). Complete necropsies were conducted on all animals, and selected organs were weighed at the scheduled necropsy. Selected tissues were examined microscopically from animals in the control and 3000 ppm groups. Tissue masses (when present), pituitary glands, and gross lesions (when present) were examined from all animals.

There were no toxicologically significant treatment related effects on mortality, clinical signs, body weight, food consumption, ophthalmology, clinical chemistry, hematology, coagulation, urinalysis, or organ weights. There were no toxicologically significant effects noted for gross or microscopic pathology.

**No significant toxicity occurred in this study and the NOAEL is 150 mg/kg/day, (1000 ppm dietary concentration) the highest dose tested. A LOAEL was not determined.**

**This study is classified acceptable/non-guideline.**

### 870.7485 DCSA Metabolism

A mixture of radio-labelled and un-labelled DCSA (5,560 dpm/µg) as a suspension in corn oil was administered by oral gavage individually to six male rats (Sprague-Dawley Crl:CD® (SD)) as a single dose at a target dose level of 100 mg/kg bw (MRID 47899502). Approximately 2 mL/kg bw of dose suspension and approximately 250 µCi/kg bw of radioactivity were administered to each animal. Rats were 57-59 days old and weighed 229-266 g at the time of dosing.

DCSA was poorly metabolized in the rat and was excreted largely unchanged primarily in urine. A summary of the distribution of radioactive residues in urine, cage wash, and faeces is given in Table 5.8-5. Unchanged DCSA accounted for approximately 82% of the administered dose. Two glucuronide conjugates of DCSA were identified, differing only in the position of glucuronidation (carboxyl moiety or phenol moiety). The position of glucuronidation of the metabolites was determined by their distinctive MS/MS fragmentation patterns – fragmentation by loss of $CO_2$ from the phenolic glucuronide indicated a free aromatic carboxyl group in that metabolite. DCSA phenolic and carboxyl glucuronides accounted for approximately 10% and 5%, respectively, of the administered dose. Several other very minor metabolites were observed, none of which constituted more than 1% of the dose. In total, more than 96% of the dose was identified.

## A.5 Inhalation Studies HEC/HED Results

Inhalation studies in Wistar rats for 6 hours/day for 5 days/week for 28 days

### Dicamba Acid

MMAD = 1.7-2.1 µm, GSD = 1.8-1.9 µm, BW = 236 g, Pulmonary RDDR = 0.590, NOAEL = 0.005 mg/L, LOAEL = 0.050 mg/L

Occupational handler: HEDs = 0.21 mg/kg/day and HEC = 2.21 mg/m$^3$
Residential handler: HED = 0.084 mg/kg/day and HEC = 2.95 mg/m$^3$
Residential outdoor post-application: HEC = 2.95 mg/m$^3$
Residential indoor post-application: HEC= 2.21 mg/m$^3$
Residential bystander: HEC = 0.53 mg/m$^3$

### Dicamba BAPMA Salt

MMAD = 1.9-2.1 µm, GSD = 1.2-3.4 µm, BW = 244 g, Extra-Thoracic RDDR = 0.190, NOAEL = NA, LOAEL = 0.0014 mg/L

Occupational handler: HEDs = 0.020 mg/kg/day and HEC = 0.195 mg/m$^3$
Residential handler: HED = 0.007 mg/kg/day and HEC = 0.26 mg/m$^3$
Residential outdoor post-application: HEC = 0.26 mg/m$^3$
Residential indoor post-application: HEC= 0.186 mg/m$^3$
Residential bystander: HEC = 0.047 mg/m$^3$

## A.6 Statistical Analysis of the Dicamba Acid Reproduction Study Pup Body Weights

### A.6.1 Mean and Standard Deviation of litter-specific average pup weight (males and females combined results)

| Mean and Standard Deviation of litter-specific average pup weight of F1 generation | | | | | | | |
|---|---|---|---|---|---|---|---|
| Dose (ppm) | N | Mean (SD) (grams) | | | | | |
| | | PND 0 | PND 4 | PND 8 | PND 12 | PND 16 | PND 21 |
| **0** | 25 | 6.29 (0.62) | 10.07 (1.67) | 19.05 (2.66) | 30.35 (3.37) | 41.53 (4.18) | 59.65 (6.24) |
| **500** | 28 | 6.29 (0.70) | 9.89 (1.94) | 18.63 (3.39) | 29.33 (3.99) | 40.01 (4.26) | 57.75 (6.37) |
| **1500** | 29 | 6.31 (0.60) | 10.26 (2.02) | 19.10 (2.91) | 29.68 (3.83) | 40.14 (5.02) | 57.30 (7.09) |
| **5000** | 26 | 5.87 (0.58) | 9.09 (1.55) | 16.00 (2.92) | 24.43 (4.31) | 33.61 (6.02) | 45.41 (8.56) |

| Mean and Standard Deviation of litter-specific average pup weight of F2 generations | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Age | Dose (ppm) | N | Mean (SD) (grams) | | | | | |
| | | | PND 0 | PND 4 | PND 8 | PND 12 | PND 16 | PND 21 |
| **F2A** | 0 | 15 | 6.59 (0.63) | 11.59 (1.23) | 21.56 (1.79) | 33.06 (2.80) | 44.49 (3.57) | 64.95 (4.09) |
| | 500 | 17 | 6.43 (0.64) | 10.75 (2.04) | 20.18 (3.44) | 31.12 (4.23) | 42.62 (4.63) | 62.48 (6.89) |
| | 1500 | 12 | 6.40 (0.67) | 10.41 (2.11) | 19.43 (3.46) | 30.23 (3.62) | 40.68 (4.43) | 58.44 (6.42) |
| | 5000 | 19 | 6.10 (0.67) | 10.38 (1.67) | 18.06 (2.90) | 26.63 (3.73) | 34.06 (4.46) | 47.89 (6.77) |
| **F2B** | 0 | 14 | 6.56 (0.64) | 10.61 (1.76) | 20.05 (3.38) | 31.45 (4.09) | 43.30 (5.32) | 61.76 (6.86) |
| | 500 | 16 | 6.61 (0.73) | 10.49 (1.68) | 19.13 (3.33) | 30.40 (4.60) | 41.69 (5.63) | 59.77 (7.22) |
| | 1500 | 14 | 6.69 (0.60) | 10.21 (1.24) | 18.16 (2.80) | 27.56 (4.62) | 37.55 (5.79) | 52.87 (8.42) |
| | 5000 | 19 | 6.12 (0.68) | 9.69 (1.98) | 16.27 (2.90) | 23.82 (4.04) | 30.50 (3.95) | 43.22 (6.33) |

Pup Body Weight Statistical Analysis Compared to the MARTA (Middle Atlantic Reproduction and Teratology Association) Historical Control Database

The results show that the PND 0 pup body weights for the MARTA historical control mean of 6.33 grams are statistically different than the 95% confidence intervals for F1 generation at 5000 ppm and F2B generation at 1500 ppm. However, only in the F1 generation at 5000 ppm is the pup body weight considered adverse at PND 0 since it is a decrease of 7.2%, before the lactation phase. In the F2B generation at 1500 ppm, the pup body weight is above the historical control average, thus not considered adverse. The concurrent control PND 0 pup body weights in the dicamba acid study were statistically identical to the MARTA historical control data base PND 0 values.

The results show that the PND 21 pup body weights for the MARTA historical control mean of 49.33 grams is statistically different than the 95% confidence intervals for all doses except the F2A generation at 5000 ppm and F2B generation at 1500 ppm. The pup body weights are only considered adverse in the F1 and F2B generations at 5000 ppm, since the pup body weights are

both decreased by over 5% (i.e. -7.9% and -12.4%, respectively) and statistically significant, relative to the MARTA historical control data.

At the 5000 ppm dose, there were adverse decreases in the F1 pup body weights at PND 0 before the lactation phase. The WIL Research Laboratories historical control database supported the MARTA database conclusions that the dicamba acid reproduction study pup body weights were still above average values at the 500 ppm and 1500 ppm doses and only below average weights at the 5000 ppm dose (DCSA reproduction study, MRID 47899517).

| PND 0 | |
|---|---|
| Mean of historical control means | 6.33 |

| Generation | Group | sample size | Dicamba group mean | Dicamba group SD | 95% CI | | p-value |
|---|---|---|---|---|---|---|---|
| F1 | Control | 25 | 6.29 | 0.62 | 6.03 | 6.55 | > 0.05 |
| F1 | 500 | 28 | 6.29 | 0.7 | 6.02 | 6.56 | > 0.05 |
| F1 | 1500 | 29 | 6.31 | 0.6 | 6.08 | 6.54 | > 0.05 |
| F1 | 5000 | 26 | 5.87 | 0.58 | 5.64 | 6.10 | < 0.05 |
| | | | | | | | |
| F2A | Control | 15 | 6.59 | 0.63 | 6.24 | 6.94 | > 0.05 |
| F2A | 500 | 17 | 6.43 | 0.64 | 6.10 | 6.76 | > 0.05 |
| F2A | 1500 | 12 | 6.4 | 0.67 | 5.97 | 6.83 | > 0.05 |
| F2A | 5000 | 19 | 6.1 | 0.67 | 5.78 | 6.42 | > 0.05 |
| | | | | | | | |
| F2B | Control | 14 | 6.56 | 0.64 | 6.19 | 6.93 | > 0.05 |
| F2B | 500 | 16 | 6.61 | 0.73 | 6.22 | 7.00 | > 0.05 |
| F2B | 1500 | 14 | 6.69 | 0.6 | 6.34 | 7.04 | < 0.05 |
| F2B | 5000 | 19 | 6.12 | 0.68 | 5.79 | 6.45 | > 0.05 |

| PND 21 | |
|---|---|
| Mean of historical control means | 49.33 |

| Generation | Group | Dicamba sample size | Dicamba group mean | Dicamba group SD | 95% CI | | p-value |
|---|---|---|---|---|---|---|---|
| F1 | Control | 25 | 59.65 | 6.24 | 57.07 | 62.23 | < 0.05 |
| F1 | 500 | 28 | 57.75 | 6.37 | 55.28 | 60.22 | < 0.05 |
| F1 | 1500 | 29 | 57.3 | 7.09 | 54.60 | 60.00 | < 0.05 |
| F1 | 5000 | 26 | 45.41 | 8.56 | 41.95 | 48.87 | < 0.05 |
| | | | | | | | |
| F2A | Control | 15 | 64.95 | 4.09 | 62.69 | 67.21 | < 0.05 |
| F2A | 500 | 17 | 62.48 | 6.89 | 58.94 | 66.02 | < 0.05 |
| F2A | 1500 | 12 | 58.44 | 6.42 | 54.36 | 62.52 | < 0.05 |
| F2A | 5000 | 19 | 47.89 | 6.77 | 44.63 | 51.15 | > 0.05 |
| | | | | | | | |
| F2B | Control | 14 | 61.76 | 6.86 | 57.80 | 65.72 | < 0.05 |
| F2B | 500 | 16 | 59.77 | 7.22 | 55.92 | 63.62 | < 0.05 |
| F2B | 1500 | 14 | 52.87 | 8.42 | 48.01 | 57.73 | > 0.05 |
| F2B | 5000 | 19 | 43.22 | 6.33 | 40.17 | 46.27 | < 0.05 |

### A.6.2 Statistical Report: Dicamba- a reproduction study – Analysis of litter-specific average pup weights versus study concurrent control groups

**Statistical methods**

Repeated-Measures Analysis of Variance (mixed-effects models) was used to analyze the litter-specific average pup weight of F1 and F2 generations on a per dam basis. (Litters of F1 generation were identified by the F0 dams' identification numbers, and litters of F2 generation were identified by the F1 dams' identification numbers.)

Since the individual pup body weights were not provided in the registrant's submission and the body weight of each of pups may be affected by the number of pups in a given dam's litter, the number of live pups in a dam on each measurement day was included in the model as covariate. Also, the number of pups in a dam's litter was standardized on post-natal day 4, so number of pups on day 0 (i.e, number of live pups born) was used as covariate for the measurement on post-natal day 4. (Results show that for each pup increase in the number of live pups in a litter, the F1 litter-specific average pup weight decreases by 0.082 grams and F2 litter-specific average pup weight decreases by 0.090 grams).

In the analysis of F1 litter-specific average pup weight, the model incorporates dose, day, interaction between dose and day, and number of live pups in the litter on the measurement day. To account for the correlation between measurements on different post-natal days of same litter, an unstructured (UN) covariance matrix was selected (which has smaller Akaike Information Criterion or AIC value compared to compound symmetric (CS) covariance matrix and autoregressive lag(1) correlation matrix (AR(1)).

In the analysis of F2 litter-specific average pup weight, the final model includes age (young: first litter/having pups at young age and old: second litter/having pups at an older age), dose, day, interaction between dose and day, interaction between age and day, and number of live pups in each specific litter on the measurement day. The three-way interaction "age-day-dose" and two-way interaction between "age-dose" were not significant and were not kept in the final model. Multiple covariance matrices were considered (UN@UN (not convergence), UN@CS, UN@AR(1), and heterogeneous/different UN for each Age). The heterogeneous covariance matrices (i.e., different UN covariance for each age) were selected based the criterion of lower AIC value.

**Results:**
Table A.6.2.a presents the results of comparison of the F1 litter-specific average pup weight. The F1 litter-specific average pup weight associated with the **high dose** (5000 ppm) was significantly lower than the **control** on post-natal days 0, 4, 8, 12, 16, and 21 (-6.4%, -9.4%, -16.2%, -19.6%, -19.2%, and 24%, respectively). The **mid-** and **low-** dose groups (1500 ppm and 500 ppm, respectively) did not differ significantly from the **control** group. Figure 1 presents the predicted curves and observed means of litter-specific average pup weight. As can be seen and was confirmed with the Dunnett's test, the average pup weight in the high-dose group differs significantly from that of the control group.

In the analysis of F2 litter-specific average pup weight data in which dams gave birth at both "young" or F2A and "old" or F2B ages, the interaction "dose*age" was not significant (p-value > 0.05 and this term was thus not kept in the final model); this indicates that the dose effect (of same dose level on same given post-natal day) on litter-specific average pup weight was not affected by the dam's age . Therefore, there is a single common dose effect on litter-specific average pup weight (on a specific post–natal day) and this can be used to appropriately represent the dose effect (on a specific post–natal day) at either age ("young" vs. "old") of the dam. However, the significant "dose*day" interaction indicates that dose effects on litter-specific average pup weight were different between post-natal days. Therefore, it is necessary for the dose effects to be estimated --- and evaluated -- separately on each post-natal day. (The significant age*day interaction indicates that the effects of post natal day on litter-specific average pup weight varied between the two ages of the dam (young and old). Note that this day effect is not related to dose effect).

Table A.6.2.b presents the results of comparisons of common litter-specific average pup weight between the dosed groups and control group. The litter-specific average pup weight in **mid-dose** group was not significantly different from the control group on post-natal days 0, 4, and 8; however, the litter-specific average pup weight in **mid-dose** group was significantly lower compared to the control group on post-natal days 12, 16, and 21 (-9.3%, -9.9%, and -11.2%, respectively). The litter-specific average pup weight in **high dose** group was significantly lower than the control on post-natal days 0, 4, 8, 12, 16, and 21 (-7.8%, -9.2%, -17.1%, -21.5%, -26.1%, and -27.4%, respectively). No significant difference was seen on any post-natal day for the **low** dose group compared to the control.

| Table A.6.2.a: Results of comparison of litter-specific average pup weight of F1 generation | | | | | | | |
|---|---|---|---|---|---|---|---|
| _Name_ | DOSE | day0 | day4 | day8 | day12 | day16 | day21 |
| LSMean (SE) | 0 | 6.60 (0.10) | 10.38 (0.32) | 18.88 (0.60) | 30.18 (0.78) | 41.36 (0.98) | 59.47 (1.42) |
| | 500 | 6.63 (0.09) | 10.23 (0.31) | 18.44 (0.56) | 29.14 (0.73) | 39.82 (0.93) | 57.56 (1.35) |
| | 1500 | 6.75 (0.10) | 10.69 (0.30) | 18.93 (0.55) | 29.51 (0.72) | 39.97 (0.91) | 57.13 (1.32) |
| | 5000 | 6.18 (0.10) | 9.40 (0.32) | 15.83 (0.58) | 24.26 (0.76) | 33.43 (0.96) | 45.21 (1.40) |
| Diff (SE) | 500 vs.0 | 0.02 (0.13) | -0.16 (0.44) | -0.43 (0.82) | -1.04 (1.07) | -1.53 (1.35) | -1.91 (1.96) |
| | 1500 vs.0 | 0.15 (0.13) | 0.31 (0.44) | 0.05 (0.81) | -0.67 (1.06) | -1.38 (1.34) | -2.34 (1.94) |
| | 5000 vs.0 | -0.42 (0.13) | -0.98 (0.45) | -3.05 (0.83) | -5.92 (1.09) | -7.93 (1.38) | -14.26 (1.99) |
| Percent (%) | 500 vs.0 | 0.36 | -1.51 | -2.30 | -3.44 | -3.71 | -3.21 |
| | 1500 vs.0 | 2.24 | 2.98 | 0.27 | -2.22 | -3.35 | -3.94 |
| | 5000 vs.0 | -6.39 | -9.43 | -16.16 | -19.60 | -19.17 | -23.98 |
| raw p-value | 500 vs.0 | 0.851 | 0.726 | 0.597 | 0.334 | 0.259 | 0.332 |
| | 1500 vs.0 | 0.241 | 0.484 | 0.949 | 0.530 | 0.304 | 0.230 |
| | 5000 vs.0 | 0.001 | 0.033 | 0.000 | 0.000 | 0.000 | 0.000 |
| Dunnett p-value | 500 vs.0 | 0.995 | 0.970 | 0.909 | 0.640 | 0.527 | 0.638 |
| | 1500 vs.0 | 0.497 | 0.819 | 1.000 | 0.860 | 0.597 | 0.478 |
| | 5000 vs.0 | 0.004 | 0.083 | 0.001 | < 0.001 | < 0.001 | < 0.001 |

| Table A.6.2.b: Results of comparison of litter-specific average pup weight of F2 generations | | | | | | | |
|---|---|---|---|---|---|---|---|
| _Name_ | DOSE | day0 | day4 | day8 | day12 | day16 | day21 |
| LSMean (SE) | 0 | 6.92 (0.09) | 11.42 (0.28) | 20.56 (0.55) | 32.01 (0.73) | 43.57 (0.86) | 62.88 (1.21) |
| | 500 | 6.91 (0.09) | 10.86 (0.27) | 19.34 (0.52) | 30.31 (0.68) | 41.76 (0.81) | 60.59 (1.14) |
| | 1500 | 6.80 (0.10) | 10.69 (0.30) | 18.89 (0.58) | 29.05 (0.77) | 39.27 (0.92) | 55.86 (1.29) |
| | 5000 | 6.38 (0.08) | 10.37 (0.25) | 17.05 (0.48) | 25.13 (0.64) | 32.19 (0.76) | 45.66 (1.06) |
| Diff (SE) | 500 vs.0 | -0.02 (0.12) | -0.56 (0.38) | -1.22 (0.75) | -1.71 (0.99) | -1.82 (1.17) | -2.29 (1.65) |
| | 1500 vs.0 | -0.12 (0.13) | -0.73 (0.41) | -1.67 (0.80) | -2.96 (1.05) | -4.30 (1.25) | -7.02 (1.76) |
| | 5000 vs.0 | -0.54 (0.12) | -1.06 (0.37) | -3.51 (0.73) | -6.88 (0.96) | -11.38 (1.14) | -17.22 (1.60) |
| Percent | 500 vs.0 | -0.22 | -4.90 | -5.91 | -5.33 | -4.17 | -3.65 |
| | 1500 vs.0 | -1.75 | -6.41 | -8.11 | -9.26 | -9.87 | -11.16 |
| | 5000 vs.0 | -7.78 | -9.24 | -17.05 | -21.49 | -26.12 | -27.39 |
| raw p-value | 500 vs.0 | 0.901 | 0.146 | 0.105 | 0.084 | 0.122 | 0.165 |
| | 1500 vs.0 | 0.344 | 0.074 | 0.037 | 0.005 | 0.001 | 0.000 |
| | 5000 vs.0 | 0.000 | 0.005 | 0.000 | 0.000 | 0.000 | 0.000 |
| Dunnett p-value | 500 vs.0 | 0.999 | 0.327 | 0.244 | 0.200 | 0.279 | 0.363 |
| | 1500 vs.0 | 0.657 | 0.177 | 0.093 | 0.014 | 0.002 | < 0.001 |
| | 5000 vs.0 | 0.000 | 0.013 | < 0.001 | < 0.001 | < 0.001 | < 0.001 |

## Supplemental Tables and Figures

Table A.6.2.c: SAS output table Type 3 Tests of Fixed Effects of the model analyzing F1 litter-specific average pup weight

| Table A.6.2.c. Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| Effect | Num DF | Den DF | F Value | Pr > F |
| **Dose** | 3 | 104 | 14.46 | <.0001 |
| **Day** | 5 | 104 | 1584.91 | <.0001 |
| **Dose*Day** | 15 | 104 | 13.42 | <.0001 |
| **npup** | 1 | 104 | 79.25 | <.0001 |
| repeated Day/subject=Dam type=un; [IDEALLY – if individual pup weights were available-- THE SUBJECT WOULD NOT BE LITTER-SPECIFIC, BUT PUP NESTED WITHIN LITTER-SPECIFIC | | | | |

Table A.6.2.d.: Statistical Analysis Software (SAS) output table Type 3 Tests of Fixed Effects of the model analyzing F2 litter-specific average pup weight

| Table A.6.2.d. Type 3 Tests of Fixed Effects | | | | |
|---|---|---|---|---|
| Effect | Num DF | Den DF | F Value | Pr > F |
| **Day** | 5 | 380 | 1979.95 | <.0001 |
| **Dose** | 3 | 76 | 30.38 | <.0001 |
| **Age** | 1 | 45 | 8.71 | 0.0050 |
| **Dose*Day** | 15 | 380 | 23.67 | <.0001 |
| **Age* Day** | 5 | 225 | 2.85 | 0.0161 |
| **npup** | 1 | 649 | 112.11 | <.0001 |
| repeated Day/subject=dam type= un group = age; | | | | |

### A.6.3 Dicamba – a reproduction study analysis of F1 body weight post-weaning period

#### Background

Table A.6.3.a below presents the available data of individual F1 generation pup body weight and the time that the data were collected.

- The data analysis was done separately for the lactation period and post-weaning period because:
  - body weight data were reported differently for the lactation period and post-weaning period and could not be combined (i.e., averaged male and female pup body weight per litter for the lactation period and individual body weights for each gender, but no litter information, for the post-weaning period)
  - For the statistics done for the lactation period, litter was the experimental subject, and number of live pups per litter was incorporated as a covariate into the analysis of lactation period; however – for the post-weaning period -- each individual pup

served as the experimental subject (no litter and no number of live pups per litter information was made available)

- The individual body weight data of female pups and male pups in post-weaning period should not be pooled together into one single analysis because there were two pups (1 male and 1 female) selected from each litter but the information to identify which pups were from the same litter was not available. In order to do a single analysis of both males and females, the litter information must be available to account for the litter effects in the model. Table 1 below summarizes the key features of both data set available for the lactation period and for the post-weaning period.

**Table A.6.3.a: Available data of F1 pup body weight and the time the data were collected**

| Time | Lactation Period (Post-natal Day) | Post-weaning Period (Post-natal Week) |
|---|---|---|
| | 0, 4, 8, 12, 16, and 21 | 4, 5, 6, 7, 8, and 9 |
| Available data | Average pup body weight per litter (all males and females together) | Individual body weight of 1 male and 1 female per litter, but no litter information was available<br>The pups have median body weight within each litter were selected |

**Caution:** Since pups for the post-weaning period were not selected randomly but instead purposely selected as the pup closest to the median of body weight within each litter, there are limitations in the interpretation of the results from the analysis using post-weaning body weight data. An effect that is statistically "not significant" at a given dose level does not necessarily mean that the dose had no significant effect on the pup body weight in general. It may be that the animal with the lowest weight in a litter which was not selected for collecting body weight data during the post-weaning period might be the animal that is most affected by the dose level.

**Statistical Methods**

Linear mixed-effects models were used to analyze the repeated-measures body weight data of the pups collected during post-weaning period. The model included Dose, Week (linear term), Week*Week (quadratic term), Week*Week*Week (cubic term), and interaction between Dose and Week. The quadratic Week*Week and cubic Week*Week*Week terms allow the models to properly account for the curvature in growth curves of the animals. Based on the AIC criterion (smaller is better), the selected models included random intercept (different pups had different body weight at beginning), random coefficient of week (different pups have different linear growth rate), and random coefficient of week*week (different pups have different curvatures between their growth curves).

**Results**

During post-weaning period, the F1 pups body weight of both median male and female in each litter in the mid dose and low dose were not significantly different from the control. However, this does not mean that the average pup body weight per litter (as in lactation period) in the mid dose and low dose were not different from the control during the post-weaning period.

The median body weight of both male and female in each litter in the high dose group was significantly lower than the control during the post-weaning period, except for the median body weight female in high dose group on week 9. Table A.6.3.b presents the mean and standard deviation of each group by week and gender. Table A.6.3.c and A.6.3.d present the body weight comparisons between the treated groups and the control group for male and female F1 pups, respectively. These comparisons were conducted using linear mixed-effects models.

**Table A.6.3.b: Mean (SD) of F1 body weight post-weaning period**

| Gender | Dose | Mean (SD) (grams) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 |
| Female | 0 | 91.93 (12.96) | 132.46 (17.55) | 170.96 (18.27) | 200.43 (22.39) | 229.50 (26.57) | 255.32 (31.74) |
| | 500 | 91.11 (10.78) | 134.61 (12.65) | 173.68 (14.22) | 203.07 (17.40) | 231.96 (20.40) | 254.21 (23.66) |
| | 1500 | 89.93 (11.48) | 132.29 (13.53) | 171.07 (17.17) | 201.11 (19.05) | 227.89 (19.98) | 254.93 (20.57) |
| | 5000 | 75.64 (9.82) | 114.79 (12.32) | 155.32 (15.02) | 186.86 (17.23) | 216.00 (21.17) | 241.29 (24.61) |
| Male | 0 | 94.82 (16.78) | 151.39 (23.04) | 215.64 (27.06) | 281.54 (32.25) | 341.68 (34.98) | 394.96 (40.08) |
| | 500 | 100.14 (12.00) | 159.50 (17.92) | 224.14 (19.92) | 292.64 (24.37) | 359.32 (27.84) | 415.14 (30.58) |
| | 1500 | 100.39 (13.10) | 157.37 (19.34) | 228.74 (24.13) | 297.64 (31.75) | 362.29 (38.38) | 419.71 (45.69) |
| | 5000 | 79.71 (16.49) | 129.21 (22.37) | 190.79 (28.79) | 254.21 (35.77) | 311.21 (46.56) | 372.41 (42.88) |

**Table A.6.3.c: Results of comparison of male pup body weight post-weaning period**

| Name | DOSE | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 |
|---|---|---|---|---|---|---|---|
| LSMean (SE) | 0 | 94.60 (2.80) | 150.55 (3.75) | 214.38 (4.78) | 280.50 (5.86) | 343.32 (6.99) | 397.24 (8.17) |
| | 500 | 100.56 (2.80) | 158.80 (3.75) | 224.93 (4.78) | 293.34 (5.86) | 358.45 (6.99) | 414.67 (8.17) |
| | 1500 | 99.70 (2.80) | 159.30 (3.75) | 226.79 (4.78) | 296.57 (5.86) | 363.04 (6.99) | 420.61 (8.17) |
| | 5000 | 79.58 (2.80) | 131.50 (3.75) | 191.31 (4.78) | 253.41 (5.86) | 312.21 (6.99) | 362.11 (8.17) |
| Diff (SE) | 500 vs.0 | 5.96 (3.96) | 8.25 (5.27) | 10.55 (6.74) | 12.84 (8.28) | 15.13 (9.87) | 17.43 (11.47) |
| | 1500 vs.0 | 5.10 (3.96) | 8.75 (5.27) | 12.41 (6.74) | 16.06 (8.28) | 19.72 (9.87) | 23.37 (11.47) |
| | 5000 vs.0 | -15.02 (3.96) | -19.04 (5.27) | -23.07 (6.74) | -27.09 (8.28) | -31.11 (9.87) | -35.13 (11.47) |
| Percent | 500 vs.0 | 6.30 | 5.48 | 4.92 | 4.58 | 4.41 | 4.39 |
| | 1500 vs.0 | 5.39 | 5.81 | 5.79 | 5.73 | 5.74 | 5.88 |
| | 5000 vs.0 | -15.88 | -12.65 | -10.76 | -9.66 | -9.06 | -8.84 |
| raw p-value | 500 vs.0 | 0.133 | 0.118 | 0.119 | 0.122 | 0.126 | 0.130 |
| | 1500 vs.0 | 0.198 | 0.098 | 0.067 | 0.053 | 0.047 | 0.042 |
| | 5000 vs.0 | <0.001 | <0.001 | 0.001 | 0.001 | 0.002 | 0.002 |

| Table A.6.3.c: Results of comparison of male pup body weight post-weaning period | | | | | | | |
|---|---|---|---|---|---|---|---|
| _Name_ | DOSE | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 |
| Dunnett p-value | 500 vs.0 | 0.305 | 0.275 | 0.275 | 0.282 | 0.290 | 0.298 |
| | 1500 vs.0 | 0.429 | 0.231 | 0.163 | 0.133 | 0.117 | 0.108 |
| | 5000 vs.0 | 0.001 | 0.001 | 0.002 | 0.003 | 0.005 | 0.007 |

| Table A.6.3.d: Results of comparison of female pup body weight post-weaning period | | | | | | | |
|---|---|---|---|---|---|---|---|
| _Name_ | DOSE | Week 4 | Week 5 | Week 6 | Week 7 | Week 8 | Week 9 |
| LSMean (SE) | 0 | 92.00 (2.18) | 134.32 (2.47) | 170.76 (2.93) | 202.27 (3.48) | 229.83 (4.11) | 254.39 (4.79) |
| | 500 | 90.61 (2.18) | 133.45 (2.47) | 170.41 (2.93) | 202.45 (3.48) | 230.53 (4.11) | 255.61 (4.79) |
| | 1500 | 90.07 (2.18) | 132.73 (2.47) | 169.51 (2.93) | 201.37 (3.48) | 229.28 (4.11) | 254.18 (4.79) |
| | 5000 | 74.75 (2.18) | 117.87 (2.47) | 155.10 (2.93) | 187.42 (3.48) | 215.77 (4.11) | 241.13 (4.79) |
| Diff (SE) | 500 vs.0 | -1.39 (3.07) | -0.87 (3.44) | -0.35 (4.08) | 0.18 (4.89) | 0.70 (5.80) | 1.22 (6.76) |
| | 1500 vs.0 | -1.93 (3.07) | -1.59 (3.44) | -1.24 (4.08) | -0.90 (4.89) | -0.56 (5.80) | -0.21 (6.76) |
| | 5000 vs.0 | -17.25 (3.07) | -16.45 (3.44) | -15.65 (4.08) | -14.86 (4.89) | -14.06 (5.80) | -13.26 (6.76) |
| Percent | 500 vs.0 | -1.51 | -0.65 | -0.20 | 0.09 | 0.30 | 0.48 |
| | 1500 vs.0 | -2.10 | -1.18 | -0.73 | -0.45 | -0.24 | -0.08 |
| | 5000 vs.0 | -18.75 | -12.25 | -9.17 | -7.34 | -6.12 | -5.21 |
| raw p-value | 500 vs.0 | 0.651 | 0.801 | 0.932 | 0.971 | 0.904 | 0.857 |
| | 1500 vs.0 | 0.530 | 0.645 | 0.761 | 0.854 | 0.924 | 0.975 |
| | 5000 vs.0 | <0.001 | <0.001 | <0.001 | 0.003 | 0.016 | 0.051 |
| Dunnett p-value | 500 vs.0 | 0.942 | 0.989 | >0.999 | >0.999 | 0.999 | 0.996 |
| | 1500 vs.0 | 0.865 | 0.939 | 0.981 | 0.996 | 0.999 | >0.999 |
| | 5000 vs.0 | <0.001 | <0.001 | <0.001 | 0.007 | 0.042 | 0.127 |

In the scatter-plot of observed group means and predicted curves of each group for F1 male and F1 female, the observed group means of each dose group were close to the group predicted curve. This result indicates that the selected model was very good in its ability to accurately characterize and describe the growth of body weight of the animals during the post-weaning period.

## Supplemental Tables and Figures

| Table A.6.3.e: SAS output table of Solution Fixed Effects in the analysis of male pup data | | | | | | |
|---|---|---|---|---|---|---|
| Effect | Dose | Estimate | Stand. Error | DF | t Value | Pr > \|t\| |
| Intercept | | 61.5338 | 13.0441 | 108 | 4.72 | <.0001 |
| Week | | -48.5249 | 6.3657 | 108 | -7.62 | <.0001 |
| Week*Week | | 17.9273 | 0.9861 | 111 | 18.18 | <.0001 |
| Week*Week*Week | | -0.9323 | 0.05021 | 332 | -18.57 | <.0001 |
| Dose | 500 | -3.2160 | 4.7512 | 332 | -0.68 | 0.4990 |
| Dose | 1500 | -9.5165 | 4.7528 | 332 | -2.00 | 0.0461 |
| Dose | 5000 | 1.0696 | 4.7516 | 332 | 0.23 | 0.8220 |
| Dose | 0 | 0 | . | . | . | . |
| Week*Dose | 500 | 2.2935 | 1.6641 | 332 | 1.38 | 0.1691 |
| Week*Dose | 1500 | 3.6541 | 1.6642 | 332 | 2.20 | 0.0288 |
| Week*Dose | 5000 | -4.0227 | 1.6641 | 332 | -2.42 | 0.0162 |
| Week*Dose | 0 | 0 | . | . | . | . |

Note: the linear growth rate of mid dose was significantly higher than the control and the linear growth rate of high dose was significantly lower than the control.

| Table A.6.3.f: SAS output table of Type 3 Tests of Fixed Effects in the analysis of male pup data | | | | |
|---|---|---|---|---|
| Effect | Num DF | Den DF | F Value | Pr > F |
| Week | 1 | 108 | 58.46 | <.0001 |
| Week*Week | 1 | 111 | 330.50 | <.0001 |
| Week*Week*Week | 1 | 332 | 344.85 | <.0001 |
| Dose | 3 | 332 | 2.01 | 0.1127 |
| Week*Dose | 3 | 332 | 8.15 | <.0001 |

| Table A.6.3.g: SAS output table of Solution Fixed Effects in the analysis of female pup data | | | | | | |
|---|---|---|---|---|---|---|
| Effect | Dose | Estimate | Stand. Error | DF | t Value | Pr > \|t\| |
| Intercept | | -155.24 | 12.8583 | 108 | -12.07 | <.0001 |
| Week | | 80.6063 | 6.2118 | 108 | 12.98 | <.0001 |
| Week*Week | | -5.3386 | 0.9758 | 111 | -5.47 | <.0001 |
| Week*Week*Week | | 0.1599 | 0.04982 | 334 | 3.21 | 0.0015 |
| Dose | 500 | -3.4838 | 4.9228 | 334 | -0.71 | 0.4796 |
| Dose | 1500 | -3.3088 | 4.9219 | 334 | -0.67 | 0.5019 |
| Dose | 5000 | -20.4414 | 4.9219 | 334 | -4.15 | <.0001 |
| Dose | 10000 | 0 | . | . | . | . |
| Week*Dose | 500 | 0.5229 | 1.1028 | 334 | 0.47 | 0.6357 |
| Week*Dose | 1500 | 0.3440 | 1.1027 | 334 | 0.31 | 0.7552 |
| Week*Dose | 5000 | 0.7979 | 1.1027 | 334 | 0.72 | 0.4698 |
| Week*Dose | 10000 | 0 | . | . | . | . |

Note: the growth curve of high dose was significantly lower (shifted down) than the control.

| Table A.6.3.h: SAS output table of Type 3 Tests of Fixed Effects in the analysis of male pup data | | | | |
|---|---|---|---|---|
| Effect | Num DF | Den DF | F Value | Pr > F |
| Week | 1 | 108 | 172.18 | <.0001 |
| Week*Week | 1 | 111 | 29.93 | <.0001 |
| Week*Week*Week | 1 | 334 | 10.31 | 0.0015 |
| Dose | 3 | 334 | 7.03 | 0.0001 |
| Week*Dose | 3 | 334 | 0.18 | 0.9073 |

## Appendix B. Physical/Chemical Properties

| Table B.1. Physicochemical Properties of the Technical Grade Test Compound: Dicamba. | | |
|---|---|---|
| Parameter | Value | Reference |
| Melting point | 114-116 EC (PAI)<br>90-100 EC (87% TGAI) | Residue Chemistry Chapter of the Dicamba RED (D317699, C. L. Olinger, 12/20/2005). |
| pH | 2.5-3.0 (87% TGAI) | |
| Density | 1.57 g/mL at 25 EC (87% TGAI) | |
| Water solubility | 0.5 g/100 mL at 25 EC (PAI) | |
| Solvent solubility | g/100 mL at 25 EC (PAI)<br>dioxane 118.0<br>ethanol 92.2<br>isopropyl alcohol 76.0<br>methylene chloride 26.0<br>acetone 17.0<br>toluene 13.0<br>xylene 7.8<br>heavy aromatic naphthalene 5.2 | |
| Vapor pressure | 3.4 x $10^{-5}$ mm Hg at 25 EC (PAI) | |
| Dissociation constant, $pK_a$ | 1.97 (PAI) | |
| Octanol/water partition coefficient, Log($K_{OW}$) | 0.1 (PAI) | |
| UV/visible absorption spectrum | neutral: 511 (275 nm)<br>acidic (pH 0-1): 1053 (281 nm)<br>basic (pH 13-14): 469 (274 nm) | |

## Appendix C. Review of Human Research

This risk assessment relies in part on data from studies in which adult human subjects were intentionally exposed to a pesticide or other chemical. These data, which include studies from Pesticide Handlers Exposure Database Version 1.1 (PHED 1.1); the Agricultural Handler Exposure Task Force (AHETF) database; the ARTF database; and the Outdoor Residential Exposure Task Force (ORETF) database, are (1) subject to ethics review pursuant to 40 CFR 26, (2) have received that review, and (3) are compliant with applicable ethics requirements. For certain studies, the ethics review may have included review by the Human Studies Review Board. Descriptions of data sources, as well as guidance on their use, can be found at the Agency website[13].

[13] http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-handler-exposure-data and http://www2.epa.gov/pesticide-science-and-assessing-pesticide-risks/occupational-pesticide-post-application-exposure

## Appendix D. International Residue Limits Summary

Dicamba (029801, 029802, 029806, 128931, 128944 & 129043; 01/16/2013)

| Summary of US and International Tolerances and Maximum Residue Limits | | | | |
|---|---|---|---|---|
| *Residue Definition*: | | | | |
| US | | Canada | Mexico[2] | Codex[3] |
| 40 CFR 180.227:<br>Plant: Compliance with the tolerance levels is to be determined by measuring only the residues of dicamba, 3,6-dichloro-0-anisic acid, and its metabolites, 3,6-dichloro-5-hydroxy-0-anisic acid, and 3,6-dichloro-2-hydroxybenzoic acid, calculated as the stoichiometric equivalent of dicamba | | benzoic acid, 3,6-dichloro-2-methoxy-, including the metabolite benzoic acid, 2,5-dichloro-3-hydroxy-6-methoxy- | | Plants: Dicamba<br>Animals:<br>sum of dicamba and 3,6-dichlorosalicylic acid (DCSA) expressed as dicamba.<br>The residue is not fat-soluble. |
| *Commodity*[1] | *Tolerance (ppm) /Maximum Residue Limit (mg/kg)* | | | |
| | US | Canada | Mexico[2] | Codex[3] |
| Cotton, undelinted seed | 3 | | | 0.04 cotton seed (*) |
| Cotton, gin byproducts | 70 | | | |
| Soybean, forage | 60 | | | |
| Soybean, hay | 100 | | | |
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| Completed: M. Negussie; 01/17/2013 | | | | |

[1] Includes only commodities of interest for this action. Tolerance values should be the HED recommendations and not those proposed by the applicant.

[2] Mexico adopts US tolerances and/or Codex MRLs for its export purposes.

[3] * = absent at the limit of quantitation; Po = postharvest treatment, such as treatment of stored grains. PoP = processed postharvest treated commodity, such as processing of treated stored wheat. (fat) = to be measured on the fat portion of the sample. MRLs indicated as proposed have not been finalized by the CCPR and the CAC.